DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE
Food and Drug Administration

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Division of Clinical Trial Design and Analysis
HFM-576

Memorandum

DATE: June 20, 2003

FROM: James Kaiser, M.D.

THROUGH: Marc Walton, M.D., Ph.D.

SUBJECT: Medical Officer's Efficacy Review
BLA STN 103976/0
Applicant: Genentech
Product: recombinant anti-human IgE
Proposed indication: Maintenance and prophylaxis of asthma exacerbations and symptoms in adolescents and adults with allergic asthma

TO: BLA STN 103976/0 file

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INTRODUCTION

Genentech's original marketing application was submitted in June 2000. As a result of interactions between Genentech and CBER, Genentech submitted more clinical trial data in December 2002. This document is an efficacy review of the marketing application to date.

The original application was a proposal to market omalizumab in patients 6 years of age and older with seasonal allergic rhinitis or asthma. Rhinitis efficacy data and overall safety data are reviewed in separate documents. Genentech no longer proposes omalizumab for use in seasonal allergic rhinitis and has revised the indication to include patients 12 years of age and older.

The proposed indication statement for omalizumab is:

> XOLAIR is indicated as maintenance therapy for the prophylaxis of asthma exacerbations and control of symptoms in adults and adolescents (12 years and above) with moderate to severe allergic asthma that is inadequately controlled despite the use of inhaled corticosteroids.

The efficacy parameter assessed in the critical efficacy trials (noted in Table 1) was the occurrence of asthma exacerbations. This parameter is also assessed in the other trials reviewed for efficacy. This document contains a brief description of asthma and the product, omalizumab. It reviews the major efficacy findings in 4 adequate and well-controlled trials and additional information provided in 2 open-label trials. Finally, it reviews information related to asthma-related clinical outcomes and to the refractoriness of the asthma in subjects studied in the controlled trials.

OVERVIEW OF ASTHMA

Asthma is defined in the National Institutes of Health Guidelines for the Diagnosis and Management of Asthma ("NHLBI Guidelines," 1997)[1], as a chronic inflammatory condition of the airways. The symptoms of asthma are recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. Obstruction to the outflow of air from the lungs, due to bronchoconstriction, occurs variably within an individual, and may reverse spontaneously or with treatment. This obstruction, which can cause wheezing, shortness of breath, and cough, may occur acutely in response to many different kinds of stimuli, and is thought to be a consequence of inflammation-induced hyperresponsiveness of the airways. Allergens may induce bronchoconstriction in susceptible persons through an interaction with IgE. Other factors, not dependent upon an immediate reaction with IgE, may stimulate bronchoconstriction, for example, aspirin and other nonsteroidal anti-inflammatory drugs, exercise, cold air, and irritants. The pathology of asthma consists of infiltration of airways with inflammatory cells, disruption of the airway lining with deposition of collagen beneath the epithelium, and microvascular leakage. There is hypertrophy of airway smooth muscle.

Asthma broadly can be characterized into childhood-onset and adult-onset disease. Childhood onset asthma is frequently found in children who are atopic, that is, with a genetic susceptibility to produce IgE toward common environmental antigens. However, in some persons who develop asthma as adults there is no family history of asthma nor are IgE antibodies to allergens found. The presence of antigen-specific IgE is not sufficient to produce asthma. Persons with elevated serum IgE or skin reactions to allergens may not have asthma.

In general, total serum IgE values increase progressively throughout childhood, level off in adulthood, and begin to drop (concordant with other immunoglobulin levels) in old age. Antigen-specific IgE will appear in the serum following allergen sensitization. IgE may actually decrease somewhat at the time of allergen exposure during the allergen season for seasonal allergens, increase after the allergen season to 2-3 fold the pre-season baseline, then come back to baseline over the

ensuing 2-3 months. There are not detailed or extensive longitudinal data on the magnitude of variability of IgE in adults in the medical literature. The variation that may be induced by other factors is also not well described (e.g., parasitic infection, other intercurrent illness, smoking, or environmental changes).

Asthma is a common disease. According to National Health Interview Survey statistics, about 27 million persons in the United States reported a physician diagnosis of asthma during their lifetime (in 1997), and about 10.5 million reported at least 1 asthmatic attack in the previous 12 months (in 1999)[3]. Approximately 25-30% of these cases were in persons less than 15 years old. Asthma can also be a mortal condition. In 1999, asthma was responsible for about 4600 deaths (about 4% of these in persons less than 15 years old). Due to the lack of a standard for the diagnosis of "allergic" asthma, the numbers of subjects with this condition are not established.

The subjective measures used to grade asthma generally include ability to sleep through the night, ability to participate in daily activities without breathlessness, the occurrence of acute worsenings called exacerbations, and exercise tolerance. Peak expiratory flow rate (PEFR) may be used for home monitoring of obstruction of breathing; in the clinic, expiratory volume in the first second of a forced expiration (FEV_1) is determined. The FEV_1 is measured using equipment found in a clinic or hospital that can be calibrated so that individuals may be compared rigorously to reference populations. Decrements in either measure signify a worsening in the ability to exhale rapidly and completely, due in asthma to reversible obstruction of the airways.

The NHLBI Guidelines categorize asthma as mild intermittent, mild persistent, moderate persistent, and severe persistent, based upon pretreatment symptoms and measurements. Figure 1 shows this codification scheme.

Figure 1. Classification of asthma according to NHLBI Guidelines

Clinical features before treatment*

	Symptoms**	Nighttime Symptoms	Lung Function
STEP 4 Severe Persistent	• Continual symptoms • Limited physical activity • Frequent exacerbations	Frequent	• FEV1 or PEF ≤60% predicted • PEF variability>30%
STEP 3 Moderate Persistent	• Daily symptoms • Daily use of inhaled short-acting beta2-agonist • Exacerbations affect activity • Exacerbations ≥ 2 times a week; may last days	>1 time a week	• FEV_1 or PEF>60% to <80% predicted • PEF variability>30%
STEP 2 Mild Persistent	• Symptoms >2 times a week but <1 time a day • Exacerbations may affect activity	>2 times a month	• FEV1 or PEF ≥80% predicted • PEF variability 20% to 30%
STEP 1 Mild Intermittent	• Symptoms ≤2 times a week • Asymptomatic and normal PEF between exacerbations • Exacerbations brief (from a few hours to a few days); intensity may vary	<2 times a month	• FEV1 or PEF ≥ 80% predicted • PEF variability <20%

* The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The

characteristics noted in this figure are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.
**Patients at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

The NHLBI guidelines state that an individual should be assigned to the highest grade in which a feature occurs. Another classification scheme, the GINA guidelines, classifies asthma as intermittent, mild persistent, moderate persistent, and severe persistent in terms of both asthma features and coincident treatment[2]. Importantly, these classifications of asthma are necessarily broad and may contain many degrees of severity. For example, a patient with severe persistent asthma with frequent hospitalizations on treatment or requiring large doses of oral corticosteroids would be considered more refractory than another patient with severe persistent asthma who had not been hospitalized or who does not require systemic corticosteroids.

There are many therapies available to treat asthma. Long-term controller medications include β-agonists, leukotriene antagonists, 5-lipoxygenase enzyme inhibitors, cromolyn sodium and nedocromil; theophylline; short term controller medications include β-agonists and ipratropium bromide. Corticosteroids have been the mainstay of controller medications of asthma; they are considered antiinflammatory agents. Oral corticosteroids are known to have systemic side effects such as suppression of growth in children, cataract formation, osteoporosis, and disturbance of glycemic control. As such, oral corticosteroids are reserved for more severely affected asthmatics. Inhaled corticosteroids are considered much safer, due to much less systemic exposure. Troleandomycin, methotrexate, cyclosporine, and other immunomodulators have been tried in cases of glucocorticoid-resistant asthma, or in severe cases in which corticosteroids may be contraindicated. These medications are given in conjunction with modification of exposure to agents in the environment or activities that are known to trigger exacerbations.

PRODUCT INFORMATION

Omalizumab is a recombinant Chinese Hamster Ovary cell-derived humanized IgG1κ monoclonal antibody. It binds to IgE and inhibits the binding of IgE to FcεRI, the high affinity receptor for IgE on mast cells and basophils. In an allergic reaction, allergens bind and crosslink the IgE bound to this receptor. Aggregation of the underlying FcεRI receptors triggers the cells to release histamine and other mediators of the allergic response. Omalizumab is meant to reduce the pool of IgE available to interact with FcεRI and thereby reduce the allergic response.

Various formulations were tested during clinical development. Initial trials were with a liquid formulation; subsequently, a lyophilized formulation was used. The trials reviewed in this document were performed with a lyophilized formulation; however, the product used in trial Q0694g, while lyophilized, differed with respect to production method, product concentration, excipients, and vial configuration.

The adequate and well-controlled critical asthma efficacy trials (trials 008 and 009) and trial 011 were conducted using omalizumab produced from a process originally described in 1997. This process was modified in 1999 to produce the to-be-marketed product. The to-be-marketed product was used in open-label trials Q2143g and IA04. Based on submitted comparability studies, CBER has judged that product produced by the to-be-marketed process is comparable to product used in trials 008, 009, 010, and 011.

DOSE SELECTION

Genentech states that the dose and dosing regimen used in the pivotal trials was selected on the basis of suggestions from previous trials that average free IgE concentrations of <25 ng/ml were correlated with efficacy and estimates from pharmacokinetic analyses of the duration of suppression

based on amount of administered product. Since the product was to be targeted to children as well as to adults, a body weight correction was added.

Comment

The a priori *relevance of serum free IgE suppression is unclear, since the release of histamine and other mediators from IgE-receptor-bearing cells is more dependent upon bound IgE than on free IgE, and the relation of bound to free IgE is complex. Other factors thought to be important in mediator release include the intrinsic ability of an individual's cells to release mediators, the activation state of cells, the degree of crosslinking of the IgE receptor by antigens as well as the expression of the receptor on cell surfaces.*

CLINICAL TRIALS CONDUCTED AND SCOPE OF REVIEW

Prior to the conduct of the critical efficacy trials in asthma, trials 008 and 009, Genentech conducted one 24-subject open-label trial studying asthma subjects as part of its population and two single-blind, placebo-controlled trials in asthma (n=34 and 12). Genentech also conducted 3 randomized, double-blind, placebo-controlled trials in asthma prior to the pivotal trial. Trial Q0630g studied 20 subjects, trial Q0634g studied 19, and Q0694g studied 317 subjects.

Table 1 shows a summary of the clinical trials that are suitable for a review of their effects on asthma symptomatology, exacerbations, and medication use. Trial Q0694g was the first asthma trial to use a lyophilized formulation but was consistent with previous trials in that it involved the intravenous route. Subsequent to this trial Novartis conducted trials coded 008, 009, and 010, 011, and IA04, which the subcutaneous route was used. Trial Q2143g, which also used the subcutaneous route, was conducted by Genentech. The open-label trials are reviewed primarily because they enrolled subjects whose concomitant medications were liberalized in comparison to the critical efficacy trials, or had worse control of their asthma. Other trials, due to their small numbers or trial designs, are not reviewed.

Table 1. Summary of major trials for efficacy

Trial	n	Ages	Design
Q0694g	317	11-50	Placebo-controlled; two dose levels; 2:1 randomization; double blind
008*	525	12-74	Placebo-controlled; double-blind stable steroid, steroid reduction, and extension periods
009*	546	12-76	Identical to trial 008
010	334	5-12	Pediatric; placebo-controlled (2:1 randomization); double-blind stable steroid, steroid reduction, and open-label extension periods
011	341	12-75	Placebo-controlled; double-blind stable steroid, steroid reduction periods
Q2143g	1899	6-76	Open-label; 2:1 randomization to omalizumab or standard treatment
IA04	312	12-73	Open-label; 2:1 randomization to omalizumab or standard treatment

*Critical efficacy trials

CLINICAL TRIAL DATA

EXPLORATORY TRIAL Q0694G

Trial Q0694g was a trial comparing two doses of omalizumab to placebo. Its design was similar to that of the subsequent pivotal trials 008, 009, and 010. It employed the intravenous route of administration of the product.

Title

Trial Q0694g was entitled "A Phase II, multicenter, double-blind, placebo-controlled study to evaluate the safety and efficacy of Anti-IgE recombinant humanized monoclonal antibody (rhumab-E25) in subjects with moderate to severe allergic asthma."

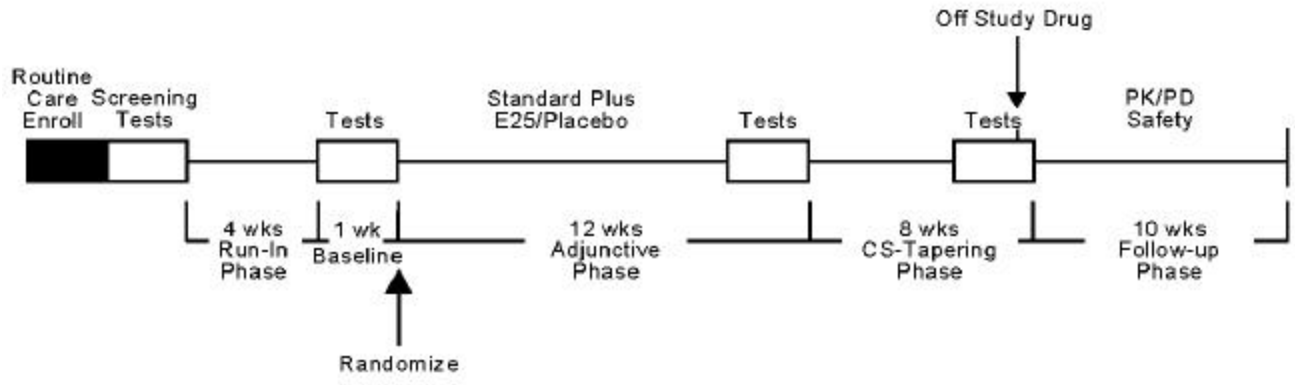
Dates of the protocol

The protocol was made final on February 23, 1996. and amended 3 times, the latest in August, 1996. This review reflects the final amended version of the protocol (see section of review on protocol modifications).

Design

This was a double-blind comparison of 2 dose levels of omalizumab to placebo in 504 subjects 12-45 years old with asthma requiring corticosteroid treatment. The primary endpoint was an overall asthma score. There were to be several phases: 4-week run-in, 1-week baseline, 12-week phase with stable corticosteroid dosing, 8-week treatment phase with protocol-defined corticosteroid tapering, and a final 10-week safety period after the last dose of omalizumab was administered (Figure 2).

Figure 2. Design of trial Q0694g



Comment

The critical efficacy trials had this basic design, but used asthma exacerbations as their primary endpoint.

Objectives

The objectives of the trial were to examine efficacy, safety, and pharmacokinetics and pharmacodynamics.

Treatment

Product and placebo were to be supplied as lyophilates to be reconstituted with water for injection, 2 ml. Each contained the excipients sucrose and histidine; after reconstitution, product was to be at 20 mg/ml.

Omalizumab or placebo was to be administered intravenously. The 1st and 2nd dose, given on days 0 and 4, were each to be ½ of the total single dose. Starting at day 7 and then every 2 weeks thereafter, the single dose was to be 0.006 or 0.014 mg/kg/IU (IgE)/ml (1.2-2.4 ml or 1.8-3.0 ml) every 2 weeks.

Comments

The dosing choices included a dose similar to the 0.016 mg/kg/IU [IgE] every 4 weeks proposed for marketing (0.012 mg/kg/IU [IgE] every 4 weeks) and one approximately twice the proposed marketed dose (0.028 mg/kg/IU [IgE] every 4 weeks). The titration of the 1st dose was abandoned in the critical efficacy trials.

Concomitant treatments

Subjects were restricted in their use of concomitant medications, as was the case in the critical efficacy trials. In trial Q0694g, subjects were only to take protocol-defined corticosteroids (inhaled triamcinolone with or without prednisone or methylprednisolone) and the β-agonist albuterol for "rescue" in case of worsened asthma. Subjects were permitted only terfenadine (Seldane) and beclomethasone nasal spray (Vancenase) for the relief of symptoms of allergic rhinitis.

Randomization and blinding

Randomization was to be 2:2:1:1 (product at 0.006 or 0.014 mg/kg/IU (IgE)/ml or corresponding placebo). Subjects were to be stratified by study center and as follows:

--Adolescents 12–17 years old requiring triamcinolone (the inhaled corticosteroid) treatment

--Adults 18–45 years old requiring triamcinolone treatment

--Adults and adolescents 12–45 requiring prednisone (oral corticosteroid) treatment

Trial medication was to be shipped open-label to sites, where the preparers were not to be involved in any other aspect of the trial.

Subject qualifications

Entry criteria were intended to select a population of asthmatic subjects with skin test reactivity to allergens that they would be exposed to, with minimal symptoms on moderate amounts of corticosteroids. Subjects with large or prolonged corticosteroid requirements were to be excluded. The asthma symptom score used for inclusion was also used as the primary endpoint data.

Inclusion criteria

- Male or females 12–45 years old on inhaled corticosteroids or oral corticosteroids
- Total serum IgE level ≤1785 IU/ml
- Skin reactivity to two or more different allergens to which there would be exposure during trial
- Documented history of reversible airway obstruction as judged by an improvement of ≥15% in FEV_1 or PEFR following β-agonist agent within the past 12 months
- Chronic use of oral (≤20 mg of prednisone daily or ≤40 mg every other day or ≤16 mg methylprednisolone daily) or inhaled (≥600 µg of triamcinolone) corticosteroids at enrollment
- If on allergy vaccination treatment, receipt of at least two constant doses that would be continued throughout participation in the trial
- If recently treated for respiratory tract infection, the treatment must have been completed at least 4 weeks prior to Screening 1
- At visit 6:

  -FEV_1 of 50%–100% of predicted for height, age, and sex

-Mean daily symptom score of ≥2.5 as measured from Day –7 to Day 0

-For subjects with a FEV_1 of ≥70% predicted, a positive response to inhalation of methacholine (PC_{20} FEV_1[Methacholine] equal to or less than 8 mg/ml)

Exclusion criteria

- Active lung diseases (e.g., bronchitis) other than allergic asthma
- Subjects whose calculated volume of administered trial agent would be <1 ml
- Use of inhaled tobacco products within the last 12 months
- History of smoking tobacco products ³10 pack-years
- Chronic daily use of oral corticosteroids for more than 12 months
- Significant active ischemic heart disease or cardiomyopathy
- Respiratory tract infection requiring treatment within the month prior to screening
- Use of any monoclonal antibody within the 6 months prior to or during the screening period
- Use of any experimental drug within 30 days prior to or during the screening period
- Receipt of escalating doses of immunotherapy
- Greater than 150% of ideal body weight for height (adults) or weight (adolescents)
- Pregnancy or lactation

Comments

The trial was intended to study asthmatics selected for skin test reactivity and exposure to an allergen or allergens. The subject population was allowed to take moderate amounts of oral corticosteroids, which would tend to allow more severe asthmatics than studied in the pivotal trials. The subject age qualification was restrictive, since asthma is a disease that occurs in the geriatric group as well.

Procedures and evaluations

The primary endpoint data, asthma symptom scores (Table 2), were recorded twice daily. These data and PEFR and medication use were recorded electronically (---------- system). There was one additional question in the adult scale, and the questions related to symptoms differed somewhat between the two scales. However, the questions overall asked about the major symptoms of asthma for both groups.

Table 2. Trial Q0694g: Symptom scores used for primary endpoint

		Adolescent		Adult	
Time	Question	Symptom	Response	Symptom	Response
Morning	1	Night waking	Frequency	Symptoms upon waking	Magnitude
	2	Night waking	Magnitude	Night waking	Magnitude
	3	Sleep disturbance	Magnitude	Sleep disturbance	Magnitude
Evening	1	Coughing	Frequency	Chest tightness/heaviness	Frequency
	2	Coughing	Magnitude	Chest tightness/heaviness	Magnitude
	3	Tiredness	Frequency	Short of breath	Frequency
	4	Tiredness	Magnitude	Short of breath	Magnitude
	5	Asthma attacks	Frequency	Wheezing	Frequency
	6	Asthma attacks	Magnitude	Wheezing	Magnitude
	7	Wheezing	Frequency	Coughing	Frequency
	8	Wheezing	Magnitude	Coughing	Magnitude
	9	Chest tightness	Frequency	Clearing throat	Frequency
	10	Chest tightness	Magnitude	Difficulty breathing out	Frequency
	11	Short of breath	Frequency	Difficulty breathing out	Magnitude
	12	Short of breath	Magnitude	Heavy breathing/fighting for air	Frequency
	13	Difficulty taking deep breath	Frequency	Heavy breathing/fighting for air	Magnitude
	14	Difficulty taking deep breath	Magnitude	-	-

- Adolescent frequency responses: 1=none of the time; 2=hardly any of the time; 3=once in a while; 4=some of the time; 5=quite often; 6=most of the time; 7=all of the time.
- Adolescent magnitude responses: 1=not bothered; 2=hardly bothered at all; 3=bothered a bit; 4=somewhat bothered; 5=quite bothered; 6=very bothered; 7=extremely bothered.
- Adult frequency responses: 1=none of the time; 2=hardly any of the time; 3=a little of the time; 4=some of the time; 5=a good bit of the time; 6=most of the time; 7=all of the time.
- Adult magnitude responses: 1=no (or none); 2=very little; 3=some; 4=a moderate amount; 5=a good deal ; 6=a great deal; 7=a very great deal.

Procedures in the trial were as follows:

- Screening, day -35
- Run-in period from weeks –4 to –2:
  --prednisone/methylprednisolone and/or inhaled triamcinolone were substituted for any previously prescribed corticosteroids, and lowest dose was determined required to maintain asthma symptoms and PEFR at levels acceptable to the subject and the investigator
  --albuterol was substituted for all other regularly prescribed sympathomimetics
  --Discontinue other asthma or rhinitis treatments with the exception of terfenadine (Seldane) and beclomethasone nasal spray (Vancenase)
- Second screening, day –7
- Baseline, days –7 to –1:
  --recording of adverse events and twice-daily recording of symptom scores, albuterol use, and PEFR
- Day 0:
  --limited physical exam, vital signs, spirometry, PEFR, methacholine challenge, symptom diary score, quality of life questionnaire, clinical lab evaluations, urine pregnancy, total and free serum IgE and product, albuterol use, concomitant medication use, and adverse events
  --First infusion
- active treatment/stable steroid phase
  --Infusions, every 2 weeks after the first week
  --Days 4, 7, then every 14 days to day 77: limited physical exam, vital signs, spirometry, urine pregnancy tests, collection of PEFR, symptom diary score, albuterol use, concomitant medication and adverse event data

--clinical lab evaluations at days 21, 49, and 77; urinalysis at day 21
--methacholine challenge at day 49
--total and free serum IgE and product at days 7, 21, and 49
--day 84: limited physical exam, vital signs, spirometry, methacholine challenge, quality of life questionnaire, collection of PEFR, symptom diary score, albuterol use, concomitant medication and adverse event data

- active treatment/corticosteroid tapering phase
  --infusion every 2 weeks (last infusion on day 133)
  --days 91-140: weekly collection of spirometry, PEFR, symptom daily score, and albuterol use
  --limited physical exam at days 105, 119, and 133
  --every 2-week urine pregnancy, clinical labs, and recording of adverse events and concomitant medications
  --total and free serum IgE and product at days 91, 133, and 140
  --day 140 only: quality of life questionnaire

During this phase, corticosteroid tapering was done as follows:

--For subjects on inhaled triamcinolone at doses ≥600 µg/d, every-2-week tapering, at a rate not to exceed 200 µg/week
--For subjects on (ingested) prednisone at ≤20 mg/d or 40 mg QOD, or (ingested) methylprednisolone, ≤16 mg/d, tapering to 0 by week 8 of the phase, at a rate not to exceed 20% per week
--For subjects on triamcinolone as well as an ingested steroid, the triamcinolone was to be continued and the ingested corticosteroid tapered
--The protocol defined reasons (asthma exacerbations) for the discontinuation of a taper:
-decrease in morning PEFR of ≥20% during 3 of 7 days since the last clinic visit
-FEV_1≥20% compared to previous FEV_1
-Worsening of asthma symptoms requiring unscheduled medical care
-≥50% increase in β-agonist use exceeding 6 puffs or 5 mg/d for ≥2 consecutive days
--Following a discontinuation of a taper, the subject was allowed to return to the pre exacerbation dose and to taper at the discretion of the investigator

- follow-up, day 210:
  --complete physical exam, vital signs, spirometry, methacholine challenge, clinical labs, urinalysis, urine pregnancy, total and free serum IgE and product

There was an early termination visit and a second termination visit 6 weeks later for subjects who withdrew from the trial early. Early termination visits were to include a complete physical exam, vital signs, spirometry, methacholine challenge, quality of life questionnaire, clinical labs, urinalysis, serum pregnancy, total and free serum IgE and product, and recording of adverse events and concomitant medications. The follow-up early termination visit was to include total and free serum IgE and product only.

Comments

The design of medication standardization with a common corticosteroid and rescue b-agonist, determination of a corticosteroid dose acceptable to the subject and investigator, followed by a stable steroid period and a subsequent steroid reduction period, was copied in the pivotal trials. That the standardized corticosteroid was different from that used in the pivotal trials is not significant.

Analytical plan

Endpoints

The primary endpoint was the change in overall symptom score from baseline to 12 weeks (stable steroid period). The overall symptom score was the mean of the 16 scores for adults and 17 scores for adolescents.

Secondary endpoints were not prioritized, and the statistical tests were not adjusted for the extreme multiplicity of analyses (for most of the following, comparisons were to be done by each week of the trial):

--means of subsets of the overall symptom score (morning, evening, frequency, and severity scores) for each week of the trial
--change in use of inhaled or oral doses of corticosteroids from baseline to end of the trial
--morning PEFR change from baseline, by week
--FEV1 , FEV1 % predicted, FVC, FVC% predicted, FEV1 /FVC, and FEF25–75, by week
--use of b-agonist medicine, morning and evening separately, weekly
--PC20 to methacholine for each test
--quality of life questionnaire (Juniper)
--pharmacokinetics and pharmacodynamics

Analytical populations

Safety analyses were to be done for all subjects who had received any trial treatment. The protocol stipulated that efficacy analyses would be performed in only those subjects with at least 4 weeks of post-randomization data. The actual final analysis of the primary endpoint, PEFR, and β-agonist use followed this rule; other efficacy data were analyzed in all subjects.

Summary of statistical methods

An ANOVA was to be performed to detect a statistical difference in response between the 2 placebo treatment schedules; if none were found, they were to be pooled for comparison to the 2 active treatment schedules.

The primary efficacy comparison was to be performed between the high-dose active group and the placebo group using ANOVA stratified by randomization category (corticosteroid use/age). The analysis was to be performed on subjects with at least 4 weeks of post-randomization data. Scores of the last week completed would be used for early dropouts.

Subset scores of the asthma symptom score were to be analyzed by ANOVA.

Corticosteroid use change was to be analyzed in terms of protocol-defined amounts of reduction (400 µg inhaled or 8 mg oral; or in categories of improved, unchanged, or worsened based on changes of 200 µg of inhaled or 5 mg of oral corticosteroids); the statistical test to be used was specified for those taking inhaled steroids only as the Wilcoxon rank-sum test.

For PEFR, the change in averages of weekly morning readings and weekly evening readings, as well as variations between each week and baseline were to be compared between treatment groups using Wilcoxon rank-sum tests. These were to exclude values taken within 4 hours of the use of β-agonists.

For spirometric comparisons, the change between baseline and the weekly score for each of the 20 weeks during the active treatment period was to be compared between treatment groups using Wilcoxon rank-sum tests.

For β-agonist use, the change from baseline in average daily score during a week for each of the weeks during the active treatment was to be compared between treatment groups using Wilcoxon rank-sum tests.

For methacholine challenge tests, the change from baseline to days 49, 91, 140, and 210 was to be compared between treatment groups using Wilcoxon rank-sum tests.

Analytical techniques for the quality of life questionnaire were not specified in the protocol.

Comments

The clinical meaning of the intertreatment comparison in asthma symptom scores for this trial was not established formally, and thus can be seen as suggestive only. The objective measures for determining efficacy are in wide use (with the possible exception of FEF_{25-75}).

Protocol modifications

The protocol was made final on February 23, 1996. It was amended 3 times, all after trial initiation on April 5, 1996:

1) May 3, 1996: The major changes in this amendment included lengthening the follow-up phase, with further efficacy, safety, and PK/PD measurements, an increase in the age of the oral corticosteroid stratum from 35 to 45, and a lowering of the adolescent age stratum to 17 years.
2) May 13, 1996. Changes were to delete the eligibility requirement for stable corticosteroid dosing for 2 months; to change the age exclusion to >45 years for all strata; and to lower the required minimum mean weekly symptom score at baseline from 4 to 3.
3) August 27, 1996: Major changes were to shorten the follow-up phase from 16 to 10 weeks and to lower the mean weekly symptom score at baseline from 3 to 2.5.

Comments

The changes made to eligibility requirements were not of sufficient magnitude to render the trial results uninterpretable. Note that the description of the protocol in this review reflects these changes.

Results: Conduct of the trial

Dates of the trial

The trial was initiated on April 5, 1996, and completed on July 1, 1997.

Early cessation of enrollment

Planned enrollment was to be 504, equally divided among adults taking inhaled corticosteroids, adolescents taking inhaled corticosteroids, and both age categories taking oral corticosteroids. When adult enrollment was exceeded, enrollment overall was stopped, although there was underenrollment in the adolescent and oral corticosteroid groups. Final enrollment was 317.

Eligibility and other protocol violations

Table 3 shows the numbers of subjects with eligibility violations. Eligibility violations were uncommon, with the exception of violations of body weight. Violations were balanced among the 3 treatment arms. These nature and extent of these violations would not be expected to substantially harm the ability to detect efficacy of the product.

Table 3. Trial Q0694g: Eligibility violations: numbers of subjects

	Placebo *n=105*	Omlzmb 0.006* *n=106*	Omlzmb 0.014* *n=106*
Age 12-45	3	3	2
Mean daily symptom score ≥2.5	6	5	5
Chronic use of oral or inhaled corticosteroid for ≥2 mo. immediately prior to enrollment	0	0	3
Documentation of improvement of ≥15% in FEV_1 with β-agonist within 12 months	2	1	1
FEV_1 50-100% predicted	2	6	4
Response to methacholine, visit 6 (those with FEV_1≥70% pred.)	2	2	2
Total serum IgE ≤1785 IU/ml	1	2	3
Well-characterized skin test reactivity to ≥2 allergens to which expected to be exposed	2	1	1
<150% of Ideal body weight	11	12	12
Less than 1 ml trial agent required, visit 6	1	0	0
Respiratory tract infection req. treatment within 1 mo. of screening	0	1	0
Other	1	0	0

* mg/kg/IU (IgE)/ml

Enrollment by site

There were 27 sites in trial Q0694g, with no one site or small number of sites dominating enrollment. The largest site enrollment, for one site, was 27 there were 12 sites whose enrollment was between 10-20 subjects inclusive, and 14 in which site enrollment was between 6 and 9 subjects inclusive.

Demographics and baseline characteristics

Table 4 shows that the treatment arms were balanced for important demographic and baseline characteristics. The trial population was primarily Caucasian and composed of slightly more females than males; 80-85% of the trial were adults. Proportionately more subjects had a history of hospitalization than in the critical efficacy trials, and this trial enrolled subjects on oral corticosteroids, unlike the critical efficacy trials. However, mean FEV_1 was similar.

Table 4. Trial Q0694g: Demographics and baseline characteristics

	Placebo *n=105***	Omalizumab 0.006* *n=106***	Omalizumab 0.014* *n=106***
Age mean (range) <18 (*n*) ≥18 (*n*)	30 (11-48) *17* *88*	30 (12-47) *16* *90*	29 (12-50) *21* 85
Sex (% male)	45	43	38
Race (% Caucasian)	86	88	78
Height (m)	1.71 (1.49-1.94)	1.69 (1.52-1.95)	1.69 (1.47-1.98)
Weight (kg)	79 (42-136)	78 (44-133)	80 (39-140)
Baseline IgE (IU/ml)	275 (19-1390)	344 (17-1646)	374 (27-1957)
Former smoker (%)	23	21	24
Age of asthma diagnosis	12 (0-38)	12 (1-44)	10 (0-41)
Hospitalized for asthma in last year, %	18	14	12
Asthma emergency room visits per year	0.9 (0-15)	0.9 (0-20)	1.1 (0-30)
Overall symptom score (0-7)	4.0 (1.5-6.5)	4.0 (2.0-6.5)	4.1 (2.4-6.5)
Inhaled corticosteroid dose in adults (g) median and range	800 (200-4000) *n=76*	800 (400-3200) *n=78*	800 (200-2400) *n=78*
Inhaled corticosteroid dose in adolescents (μg) median and range	800 (400-1600) *n=17*	800 (600-2000) *n=14*	800 (400-2600) *n=19*
Oral corticosteroid dose (mg), median and range	10.0 (2.5-40) *n=12*	10.0 (5.0-20.0) *n=14*	10.0 (5.0-10.0) *n=19*
Stratification variables Adolescents on inhaled triamcinolone (n) Adults on inhaled triamcinolone (n) Adults and adolescents on (oral) prednisone (n)	 17 76 12	 14 78 14	 19 78 9
Morning PEFR (l/min)	384 (150-620)	380 (151-626)	378 (143-599)
FEV_1, % predicted	70 (32-101)	71 (29-115)	73 (34-129)
β-agonist in subjects using MDI only (puffs)	8.2 (2.0-16.8) *n=63*	8.8 (2.0-22.7) *n=66*	8.8 (2.0-37.7) *n=73*

Data are mean and range except where noted otherwise
* mg/kg/IU (IgE)/ml
**som e cells have smaller subject numbers, as shown

Comments

The severity of some of the subjects was greater than that in the pivotal trials, since investigators felt the need for oral corticosteroid treatment, and medical care visits were greater in some. The primarily Caucasian makeup of the population mirrored that of the pivotal trials. Geriatric subjects were excluded.

Premature discontinuations

Table 5 shows the reasons for discontinuation from treatment or the trial. Discontinuations from the trial were slightly more common among placebo subjects (about 15% vs. 10% (omalizumab lower dose) or 7% (omalizumab higher dose)). The reasons for discontinuation were fairly well balanced among the treatment arms. Some subjects discontinued from the trial after completion of

the trial treatment period, so the numbers of subjects discontinuing from the trial is greater than the number discontinuing from treatment.

Table 5. Trial Q0694g: Discontinuations: numbers of subjects

	Placebo *n=105*	Omlzmb 0.006* *n=106*	Omlzmb 0.014* *n=106*
Discontinued from trial agent	14	10	7
Due to adverse event	2	3	4
Other reason[1]	12	7	3
Discontinued from trial	16	11	7
Due to adverse event	5	3	3
Due to subject decision	5[1]	5[2]	1[3]
Due to loss to follow-up	3	3	3
Due to physician decision	2	0	0
Due to pregnancy	1	0	0

* mg/kg/IU (IgE)/ml
[1] reasons not described
[2] 2 reasons not described; others not related to treatment
[3] 1 not improving; 4 unrelated to treatment
[4] parental decision not described

Comment

The nature and extent of the discontinuations would not be expected to influence the overall judgment of the effect of omalizumab in this trial.

Interim efficacy analyses of trial

Analyses of trial results were performed by Genentech at the end of the stable steroid and steroid reduction phases prior to full completion of study. Data managers, computer programmers, and the statistician were unblinded to treatment assignments for these analyses; other project personnel were not allowed to know individual treatment assignments but were allowed to know the results unblinded by treatment group. Genentech states that treatment assignments were kept from investigators and subjects throughout the trial.

Comment

The unblinding of results could have affected the trial's primary assessment of efficacy, which relied on subjective judgments, during the steroid reduction period. Even the spirometric outcome measures might be affected, since they depend on the efforts of subjects and trial personnel.

Results: Efficacy

Analytical populations

Genentech pooled the placebo groups according to their plan stipulating this manipulation in the event that there was no statistical difference in the primary endpoint between the two placebo dosing regimens. Baseline mean (± std. error) placebo scores in the low-dose and high-dose groups were almost identical at 3.98 ± 0.15 and 3.97 ± 0.14; week 12 differences from baseline similar at –0.87±0.14 and –0.79±0.16, and week 20 differences from baseline similar at –1.0±0.18 and –1.06±0.2.

Primary efficacy results

Genentech conducted an ANCOVA analysis on the intent-to-treat population, with last observation carried forward, as an exploratory analysis. Because this type of analysis is subject to

less bias than the planned primary (all subjects with at least 4 weeks of post-randomization data), it will be presented instead of the presented primary analysis. Table 6 shows the results.

Table 6. Baseline Overall Symptom Score and reduction*

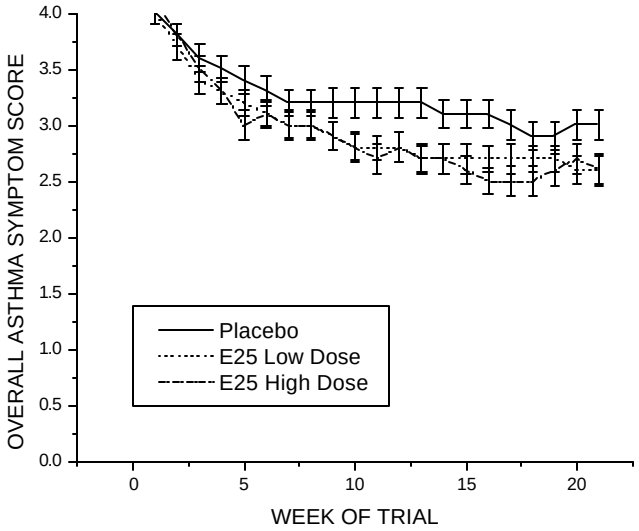
	Placebo *N=100*	Omalizumab 0.006** *N=103*	Omalizumab 0.014** *N=103*
Baseline Mean ± std. error	4.0 ± 0.1	4.0 ± 0.1	4.1 ± 0.1
Week 12 reduction Mean ± std. error *p-value*	0.8 ± 0.12	1.3 ± 0.12 *0.003*	1.3 ± 0.12 *0.004*
Week 20 reduction Mean ± std. error *p-value*	1.0 ± 0.13	1.3 ± 0.13 *0.09*	1.4 ± 0.13 *0.03*

* ITT population
**mg/kg/IU (IgE)/ml

Results of Genentech's primary analysis, on subjects with at least 4 weeks of post-randomization data, were virtually identical (not shown).

Treatment with omalizumab caused a small difference from placebo in the mean overall score, which was similar between the two active groups. Figure 3 shows the results as mean overall symptom score for those subjects with data at different time points in the trial. As stated in "Unblinding of the trial," aggregate results were made known to Genentech personnel after analysis of the week 12 (stable steroid period) results, with a potential for biasing steroid reduction period results. Missing data were approximately equally distributed across treatment groups.

Figure 3. Trial Q0694g: Overall asthma symptom scores (subjects with at least 4 weeks of data collected)



Numbers of subjects with overall symptom scores (selected weeks)

	week 0	week 5	week 10	week 15	week 20
Placebo	105	99	88	83	78
Omalizumab low dose	106	101	92	91	87
Omalizumab high dose	106	101	96	94	84

Comment

Both the pooled placebo groups and omalizumab groups improved during the trial. The difference from placebo in the change in symptom score was approximately 0.5 symptom score units, consistent with the magnitude of changes seen in the critical efficacy trials. The clinical meaning of the intertreatment differences seen in total score were not clarified in the submission.

Secondary efficacy results

- *Subset scores (morning, evening, frequency, and magnitude) of symptom diary*

These were examined by Genentech but will not be reviewed here, as they would not add substantially to the understanding of the efficacy of the product, given the limitations of the primary endpoint itself (lack of established meaning of the intertreatment differences).

- *Corticosteroid reductions*

Genentech examined reductions in corticosteroid use among subjects with inhaled only corticosteroid use at baseline using imputation of the last observation carried forward for those who discontinued (Table 7). A somewhat larger proportion of subjects on active treatment were able to discontinue their use of corticosteroid entirely, a number that was similar in the two active dose groups.

Table 7. Trial Q0694g: Inhaled corticosteroid reductions (subjects on inhaled corticosteroid only)

	Placebo *n=93*	Omalizumab 0.006* *n=92*	Omalizumab 0.014* *n=97*
Baseline median dose (μg)	800	800	800
Median reduction (%)	25	41 *p=0.022*	50 *p=0.039*
Subjects with >50% reduction	35 (38%)	45 (49%) *p=0.122*	49 (51%) *p=0.074*
Subjects with 100% reduction	11 (12%)	21 (23%) *p=0.048*	17 (18%) *p=0.268*

*mg/kg/IU (IgE)/ml

P-values compare the omalizumab groups to placebo using the Wilcoxon rank-sum test for continuous endpoints and Pearson χ^2 test for binary endpoints.

The numbers of subjects who were receiving oral corticosteroids at baseline was quite small (12 placebo, 14 low-dose omalizumab, and 9 high-dose omalizumab) so conclusions regarding this group are tenuous. However, there was a trend toward benefit in this group: the median percents reduction in oral corticosteroids in the placebo, low-, and high-dose groups were 0, 65% (p=0.106 compared to placebo), and 50% (p=0.045 compared to placebo).

Comment

The reduction in oral corticosteroid dosing was not seen in trial 011, which randomized 100 subjects to placebo or to the proposed regimen of omalizumab in a subcutaneous dosing.

- *Morning PEFR,*

Changes in PEFR were small in placebo and omalizumab groups. Table 8 shows results reported in subjects with at least 4 weeks of post-randomization data.

Table 8. Trial Q0694g: Morning PEFR, l/min (mean ±std. error)

	Placebo *n=100*	Omalizumab 0.006* *n=102*	Omalizumab 0.014* *n=103*
Baseline	383 ± 9.3	380 ± 9.1	379 ± 8.4
Week 12 increase	11.3 ± 4.6	18.6 ± 4.6 *p=0.10*	30.7 ± 5.4 *p=0.01*
Week 20 increase	10.2 ± 5.7	20.8 ± 5.9 *p=0.05*	29.9 ± 5.7 *p=0.02*

*mg/kg/IU (IgE)/ml

P-values compare the change from baseline between Omalizumab groups and placebo using the Wilcoxon rank sum test.

Smaller changes were seen in the evening PEFR, but the treatment effect was present, with an apparent positive relationship to dose.

- *Change from baseline in FEV_1*

There were no clinically important or statistically significant differences during the trial between either treatment group and placebo in change in FEV_1 from baseline to the end of the stable steroid or steroid reduction phase (Table 9).

Table 9. Trial Q0694g: Morning FEV_1% predicted

	Placebo *n=100*	Omalizumab 0.006* *n=102*	Omalizumab 0.014* *n=103*
Baseline	70 ±1.5	71 ±1.6	73 ±1.6
Week 12 increase	1.0 ±1.4	2.1 ±1.3 *p=0.493*	1.9 ±1.2 *p=0.806*
Week 20 increase	0.7 ±1.6	1.4 ± 0.98 *p=0.430*	1.2 ±1.2 *p=0.664*

*mg/kg/IU (IgE)/ml
P-values compare change from baseline between active and placebo groups using the Kruskal-Wallis test.

- *Rescue albuterol use*

Genentech analyzed usage of albuterol in terms of puffs per day, excluding the approximately 1/3 of subjects who also inhaled nebulized albuterol (Table 10). There was an apparent dose relation of effect, with statistical significance reached only in the high-dose group. At the end of the stable steroid period, the difference in usage between placebo and the high-dose group was about 1 puff per day; at the end of the steroid reduction period, about 2 puffs per day.

Table 10. Q0694g: Total daily puffs of albuterol rescue by metered dose inhaler*

	Placebo *n=63*	Omalizumab 0.006** *n=66*	Omalizumab 0.014** *n=73*
Baseline	8.2 ± 0.4	8.8 ± 0.5	8.8 ± 0.7
Week 12 reduction	0.8 ±0.4	1.2 ± 0.4 *p=0.24*	1.8 ± 0.6 *p=0.02*
Week 20 reduction	0.1 ± 0.4	0.8 ± 0.5 *p=0.11*	2.0 ± 0.6 *p=0.02*

*excludes those who also took nebulized albuterol
***mg/kg/IU (IgE)/ml
P-values compare change from baseline between active and placebo groups using the Kruskal-Wallis test.

Comments

Two puffs is the average treatment of a single worsening of breathing by albuterol by metered dose inhaler, so the difference of the averages comparing high-dose to placebo was equivalent to one episode of wheezing a day. This was a slightly higher effect than was seen in the pivotal trials. The selection effect of excluding from analysis those on nebulized albuterol is unclear, and lends some ambiguity to the interpretation of these results.

- *Response to methacholine*

A small subset of subjects received the methacholine challenge tests (28 placebo, 31 low-dose omalizumab, and 21 high-dose omalizumab), and there were no notable trends in effect from baseline or between groups during the trial.

- *Asthma exacerbations*

This was not a protocol-defined endpoint, and there is no definition of an exacerbation for this endpoint in Genentech's analysis. However, due to its importance in relation to the primary endpoint of the pivotal trials, these data will be summarized here. The data suggest that the treatment reduced the number of asthma exacerbations reported as adverse events, to the same level regardless of dose. The data also suggest that asthma exacerbations that required treatment with oral corticosteroids were reduced by the same extent regardless of treatment dose, among those taking only inhaled corticosteroids at baseline.

Table 11. Q0694g: Asthma exacerbations reported as adverse events

	Placebo	Omalizumab 0.006*	Omalizumab 0.014*
Subjects with asthma exacerbations (%)[a]	47/105 (45%)	30/106 (28%) *p=0.01*	32/106 (30%) *p=0.03*
Mean asthma exacerbations/ subject [b,c]	0.77	0.41 *p=0.01*	0.44 *p=0.02*
Subjects on inhaled corticosteroids at baseline with asthma exacerbations treated with oral corticosteroids (%)[a]	26/93 (28%)	15/92 (16%) *p=0.06*	13/97 (13%) *p=0.01*
Mean asthma exacerbations treated with oral corticosteroids in subjects on inhaled corticosteroids at baseline[b, c]	0.38	0.21 *p=0.05*	0.22 *p=0.02*

*mg/kg/IU (IgE)/ml
[a] ITT population; p-values: Pearson χ^2 test
[b] P-values: Wilcoxon rank-sum test
[c] total number of exacerbations divided by the total number of subjects

- *Juniper quality of life questionnaire*

The quality of life questionnaire used in this trial was the same as that used in the pivotal trials (see discussion of the overall design in the review of trials 008 and 009). Scores are presented by Genentech for adults and adolescents separately (Table 12).

During the trial all groups achieved higher score. The maximal difference in the mean score was 0.5 (adults, 0.014 mg./kg./IU (IgE)/ml vs. placebo).

Table 12. Q0694g: Overall Juniper quality of life questionnaire scores (mean ±s.d.)

		Placebo	Omalizumab 0.006*	Omalizumab 0.014*
Adults		*n=88*	*n=90*	*n=85*
	Baseline	3.9 ± 0.8	3.7 ± 0.9	3.7 ± 0.8
	Week 12	4.7 ± 1.1	4.9 ± 1.1 *p=0.01*	5.1 ± 1.3 *p<0.001*
	Week 20	4.7 ± 1.1	4.9 ± 1.2 *p=0.01*	5.2 ± 1.2 *p<0.001*
Adolescents		*n=14*	*n=13*	*n=18*
	Baseline	3.7 ± 1.1	3.9 ± 1.2	3.5 ± 1.3
	Week 12	5.0 ± 1.1	5.4 ± 1.1 *p=0.66*	5.4 ± 1.2 *p=0.20*
	Week 20	5.4 ± 1.2	5.8 ± 1.2 *p=0.76*	5.5 ±1.0 *p=0.64*

**mg/kg/IU (IgE)/ml

Antibody

Because the marketed product is for subcutaneous administration, the results of the antibody determinations in trial Q0694g were not reviewed.

Summary: Efficacy in supportive trial Q0694g

Interpretation of the results of this trial during the steroid reduction phase is compromised by unblinding of results to Genentech personnel prior to this phase, with the potential for biases in reporting and measurement of effects. In addition, production method changes between the material used in Q0694g and trials 008-010 lessen the relevance of these data to those developed in the latter trials. However, results in Q0694g were consistent with those in trials 008-010. Intertreatment differences in the changes in symptom scores were small; equivocal differences were seen in

different measures of pulmonary function. Intravenous omalizumab treatment was associated with lower asthma exacerbations rates. These effects were consistent with those in the pivotal trials.

CRITICAL EFFICACY TRIALS 008 AND 009

Trials rhuMAb-E25 01 008 and 009 were the pivotal trials for adolescents and adults in asthma. They were nearly identical in design and will be reviewed in parallel.

Titles

Trials 008 and 009 were both entitled "A Phase III, 7-month, randomized, double-blind, parallel-group, placebo-controlled, multicenter study with a 5-month blinded extension period to assess the efficacy, safety, tolerability, steroid-reduction, pharmacokinetics, and pharmacodynamics of subcutaneous rhuMAb-E25 in adolescents and adults with moderate to severe allergic asthma requiring daily treatment with inhaled corticosteroids."

Dates of the protocols

The protocols were made final on November 21, 1997 and amended formally on May 7, 1998. This review reflects the final amended version of the protocol, with other changes as noted (see section of review on protocol modifications).

Design

Trials 008 and 009 were designed as double-blind comparisons of subcutaneously administered omalizumab or placebo in asthmatic subjects with skin-test sensitivity to common allergens. Planned enrollment was 550 subjects each.

Table 13 is a schematic of the trials. Screening was performed at week –7, followed by a run-in period of 4-6 weeks during which the dose of inhaled corticosteroid (Beclomethasone dipropionate, or BDP) was to be stabilized. The evaluation "core" period was divided into a 16-week period during which corticosteroids were to be held stable followed by a corticosteroid reduction phase of an additional 16 weeks. Following this were 5 months of double-blind extension, during which subjects were to remain on their assigned treatment, but concomitant medications and the dose of prescribed corticosteroid were to be liberalized. A follow-up evaluation was performed after cessation of treatment for safety evaluations and the determination of antibodies to the product.

Table 13. Schematic of Trials 008 and 009

	Screening	Run-in	Corticosteroid Stabilization	Corticosteroid reduction	Extension	Follow-up
Visit	1	2*	3-7*	7-13	13-19	20
Week	-7	-6/-4 to 0	0-16	16-28	28-52	64
Treatment	none	none	Randomized double-blind omalizumab or placebo			none
Inhaled Corticosteroids	BDP ≥420 µg/day or equivalent	BDP 420-840 µg/day	BDP stable dose	tapered BDP dose up to 8 wks, BDP stable dose 4 wks	BDP treatment as appropriate	any

*Visit 2 was divided biweekly into 2.1, 2.2, and 2.3. Visits 3-6 were divided biweekly into 3, 3.1, 4, 4.1, etc.
Note: BDP is beclomethasone dipropionate

Objectives

The objectives of the trials were to examine efficacy, safety, and pharmacokinetics and pharmacodynamics of omalizumab.

Trial treatments

Omalizumab was to be supplied as a lyophilate containing 150 mg omalizumab, 108 mg sucrose, 1.3 mg L-histidine, 2.1 mg L-histidine HCl monohydrate, and 0.4 mg polysorbate 20. It was to be reconstituted with water for injection.

Omalizumab was to be administered subcutaneously at a dose normalized for body mass and serum IgE level, approximately 0.016 mg/kg/IgE [IU/ml] per month. These doses were to be selected from a chart of body mass and serum IgE categories (Table 14). Dosing in a given cell of the table was calculated to provide 0.016 mg/kg/IgE for the maximal body mass and serum IgE level that the cell referred to; that is, most subjects were to receive more than the idealized normalized dose. No subject was to receive more than 375 mg as a single administration; if a calculated monthly dose were more than 300 mg, the dose was given as 2 equal doses every 2 weeks. If a subject's body mass and serum IgE demanded a dose of omalizumab higher than 750 mg per month, he or she would be excluded from the trial.

Table 14. Dosing table for trials 008 and 009 (milligrams/dose)

Baseline IgE (IU/ml)	Body mass (kg)					Frequency of dosing
	30-60	>60-70	>70-80	>80-90	>90-150	
>30-100	150	150	150	150	300	Q4wk
>100-200	300	300	300	300	225	Q2wk
>200-300	300	225	225	225	300	
>300-400	225	225	300	300		Not dosed
>400-500	300	300	375	375		
>500-600	300	375				
>600-700	375					

Comments

This dosing goal of a minimum 4-weekly dose was replicated in every important trial of efficacy. In the pediatric trial the IgE limit was extended upwards, and in the open-label trial Q2143g, the upper body mass category was split (see review of that trial), but the overall scheme has been consistent.

Concomitant medications

Concomitant medications were to include inhaled BDP and "rescue" inhaled albuterol (trial 009 used salbutamol as rescue). If a subject were to have taken allergy vaccination therapy (desensitization immunotherapy) for ≥3 months of stable doses before visit 1, he or she was to maintain this treatment unchanged throughout the trial. Short- or medium-acting antihistamines were allowed for the treatment of allergic rhinitis.

The protocol prohibited all the major medications used to treat moderate asthma (the subjects would not be expected to use medications for glucocorticoid resistant asthma): oral, parenteral, nebulized, or aerosol β-2agonists (excluding the prescribed albuterol rescue medication), theophyllines, cromolyn sodium or nedocromil sodium, oral or parenteral corticosteroids (except for treatment of asthma exacerbation as defined above), leukotriene receptor inhibitors, 5-lipoxygenase enzyme inhibitors, oral/inhaled anticholinergics, long-acting antihistamines, β-adrenergic antagonist medications, or any investigational, experimental, or nonapproved drugs. Subjects were not to start desensitization immunotherapy for allergies.

Comment

Excluding a large number of concomitant medications limited the trial population to those who could be managed reasonably on modest doses of inhaled corticosteroids alone.

Randomization and blinding

Randomization was in balanced blocks (n=4) of patient numbers for each of the two treatment groups within each center.

Treatments were to be shipped to sites open-label. Each site was responsible for reconstitution of treatments prior to administration and for ensuring that personnel responsible for reconstitution and administration were not be involved in subject evaluations. Inspection of sites by Biologics Inspection and Monitoring revealed no cause for concern due to unblinding.

Subject qualifications

Inclusion and exclusion criteria were designed to ensure that subjects were within given IgE and weight ranges so that they could be dosed according to the dosing table provided. In addition, subjects had to have a skin test reaction to a common allergen to which they would be exposed. They were to have symptomatic asthma while on a stable dose of corticosteroid and bronchodilators.

Inclusion criteria

- Male and female, aged 12-75 years, willing to sign informed consent
- Diagnosis of allergic asthma ≥ 1 year duration who also meet the following criteria:
    - Meet standards of the American Thoracic Society
    - A positive prick skin test (e.g., +3 reaction) to at least one of the following allergens to which patients are exposed to during the trial: Dermatophagoides farinae, Dermatophagoides pteronyssinus, cockroaches (whole body), dog or cat.
    - Total serum IgE level ≥ 30 to ≤ 700 IU/ml and body weight ≤ 150 kg.
    - ≥12% increase in FEV1 over baseline value within 30 minutes of taking one or two puffs of albuterol (90 µg/puff)
    - Baseline FEV1 ? 40 to ≤ 80% of the predicted normal value, demonstrated 6 or more hours after short-acting β-2-agonist or 72 hours or more after long-acting β-2-agonist
    - Mean daily total symptom score of ≥ 3.0 during the last 14 days prior to randomization*
    - Requiring treatment with inhaled corticosteroids in doses equivalent to beclomethasone 420 to 840 µg per day, for ≥3 months prior to randomization; and as needed or regular use of bronchodilator therapy.
- No significant change in the regular asthma medication, no acute asthma exacerbation requiring corticosteroid rescue for at least 4 weeks prior to run-in period (Visit 2.1)
- Able to use the Mini-Wright peak flow meter for the measurement of peak flow, and a metered-dose inhaler (MDI) for administration of albuterol rescue medication.

**The asthma symptom score grades asthma symptoms by 3 periods of a day:*

- *morning symptoms (0=no, 1=yes)*
- *nocturnal symptoms*

  0=I did not wake up because of any breathing problems.

  1=I awoke once because of my breathing problems, but did not use my rescue medication.

  2=I awoke once because of my breathing problems, but my rescue medication controlled my symptoms.

  3=I awoke more than once because of my breathing problems, but my rescue medication controlled my symptoms.

  4=I had difficulty sleeping because of my breathing problems even though I used my rescue medication.
- *Daytime symptoms*

  0=No symptoms at all; unrestricted activity.

1=Symptoms caused little or no discomfort; unrestricted activity.
2=Symptoms caused some discomfort, at times limiting strenuous activity.
3=Symptoms caused moderate discomfort and sometimes limited routine activity.
4=Symptoms occurred at rest, caused marked discomfort, and usually limited routine activity.

The maximum score is 9, minimum is 0

Exclusion criteria (selected items)

- Previous treatment with rhuMAb-E25 or prior randomization into the trial
- Hypersensitivity to any ingredients of product or to trial medication drugs related to trial medication
- History of acute infectious sinusitis or respiratory tract infection within 1 month prior to Visit 1
- Aspirin or other nonsteroidal anti-inflammatory drug-related asthma
- Active lung disease other than allergic asthma (e.g. chronic bronchitis)
- Elevated serum IgE levels for reasons other than atopia (e.g., parasitic infections, hyperimmunoglobulin E syndrome, allergic bronchopulmonary aspergillosis)
- Currently taking allergy vaccination therapy (desensitization immunotherapy), with less than 3 months of stable maintenance doses prior to Visit 1
- Use of antihistamines, leukotriene receptor inhibitors, 5-lipoxygenase inhibitors, cromolyn sodium or nedocromil sodium, anticholinergics, theophyllines, β2-agonists, oral or intravenous corticosteroids, or treatments for corticosteroid-resistant asthma (methotrexate, gold salts, cyclosporin or troleandomycin)
- Use of β-adrenergic antagonist medications (e.g., propranolol)
- Smoking within 2 years of Visit 1 or history of smoking ≥ 10 pack years
- Clinically significant abnormality on 12-lead ECG at Visit 1
- Abnormal chest X-ray (excluding changes consistent with asthma) within the last 12 months of Visit 1
- Significant systemic disease, or a history of such disease (e.g., cancer, infection, hematological, renal, hepatic, coronary heart disease or other cardiovascular diseases, endocrinologic, or gastrointestinal disease) within the previous 3 months
- Clinically significant laboratory abnormalities and evaluations at Visit 1
- Treatment with an experimental, non-approved drug or investigational drugs within the past 30 days

Comments

Subjects were enrolled into the trial with a diagnosis of asthma in association with skin test reactivity to common allergens. The exclusion criteria were extensive, and narrowed the population to those effectively treated with a narrow spectrum of medications. This is a concern for both the safety and efficacy evaluation. The excluded medications do not define well-recognized pathogenetic subtypes of allergic asthma.

According to the NHLBI Guidelines, based on FEV_1 alone these subjects would be expected to have moderate persistent or severe persistent asthma. However, the protocol did not limit the selection of subjects to those with a history of moderate to severe symptomalogy, those with a history of frequent medical care, or those with need for additional concomitant medications beyond medium doses of corticosteroids. In this sense, the protocol was not designed to study severely ill asthmatics.

Procedures and evaluations

Recognition of asthma exacerbations and management of exacerbations

Recognition of worsenings of asthma and their management were critical to this trial. Subjects were to notify their investigator for evaluation for any of the following

−− worsening of asthma at any time requiring an urgent (unscheduled) visit for medical care

−− PEFR <50% of patient's personal best −− a decrease in morning PEFR of ≥20% on ≥2 of 3 successive days, compared to the lowest morning PEFR in the week prior to Visit 3

−− a ≥50% increase in 24-hour rescue medication use on ≥2 of 3 successive days, compared to the last week prior to randomization (must exceed 8 puffs)

−− ≥2 of 3 successive nights with awakenings due to asthma symptoms requiring rescue medication

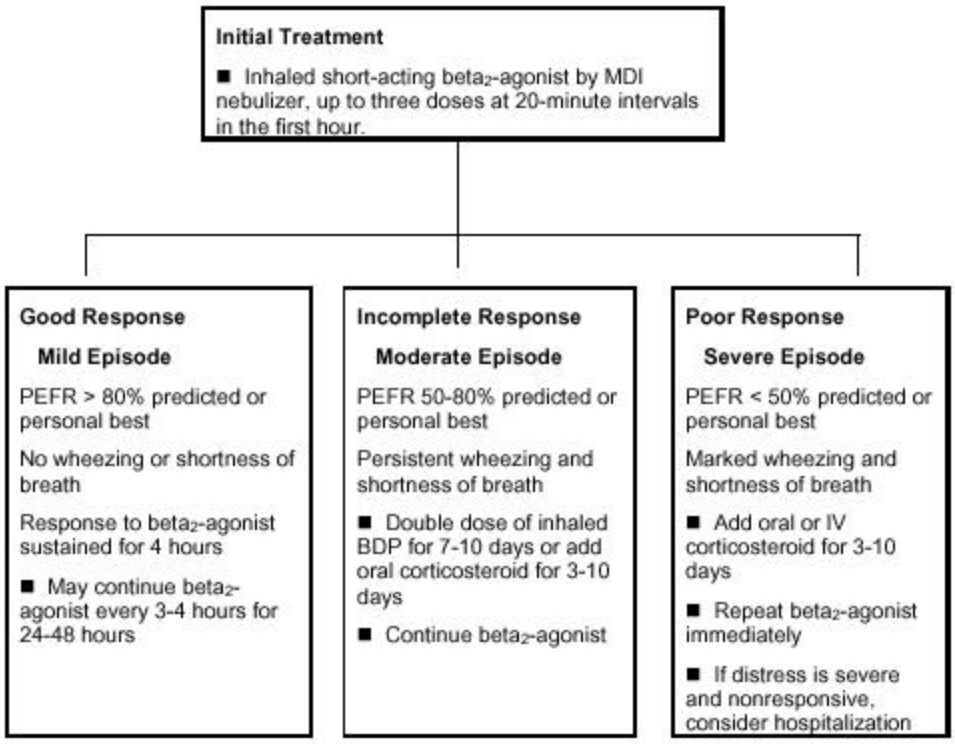
Subjects were to monitor their PEFR at home twice a day. In addition, the protocol instructed investigators to evaluate a subject for treatment if a subject were to have a ≥20% decrement in FEV_1 compared to the baseline measurement at visit 3. Subjects were to be treated as deemed appropriate by the investigator.

Comments

Case report forms, filled out at the treatment site, required that the site check whether one or more of these criteria was met. In addition, an "other" criterion was allowed. This is reasonable, since asthma exacerbations are not fully described by the criteria listed. The primary endpoint of the trial was defined not by these criteria, but by the doubling of prescribed inhaled corticosteroids or the institution of oral corticosteroids.

Treatment guidelines were provided that were minor modifications of the NHLBI Guidelines (Figure 4).

Figure 4. Treatment of asthma exacerbations during stable steroid phase



Comments

The guidelines in Figure 4 differ from the NIH guidelines in that the protocol guidelines recommend corticosteroid administration for more severe episodes, i.e., doubling inhaled corticosteroid dosing for the "moderate episode" category, while the NIH guidelines recommend this step in the case of a "mild episode," and addition of oral corticosteroids for severe episodes, while the NIH guidelines recommend them for moderate and severe episodes. The protocol guidelines include the step of intravenous corticosteroids for severe episodes, while the published guidelines do not mention this step explicitly, instead recommending proceeding to an emergency department. These differences are minor, and were guidelines only, not with binding effect.

Screening (visit 1)

At screening (7 weeks prior to the evaluation period) medical and allergen history, complete physical examination, checking of the inclusion and exclusion criteria, 12-lead ECG, CXR, skin prick test, and reversibility bronchial obstruction were assessed.

Run-in (visits 2.1-2.3, every 2 weeks for 4-6 weeks)

In order to standardize corticosteroid treatment, at visit 2 all subjects were switched to inhaler treatment twice a day with BDP, 84 µg/puff, at a total dose comparable to the corticosteroid the subject had been on prior to the trial. The dose was kept the same or adjusted at week 2 of the run-in period to achieve a level of symptoms and PEFR "acceptable" to the subject and investigator. The total time a subject was to be on a stable dose was 4 weeks; if an adjustment were to be required, the length of the run-in period would be extended to 6 weeks. At the end of the run-in period, patients who continued to be symptomatic (mean total symptom score ≥ 3 on the last 14 days prior to Visit 3) would be randomized.

Vital signs, spirometry, adverse experiences, and concomitant medications were determined during this period.

Stable steroid phase, visits 3-7, day 0- week 16

Subjects were to remain on the dose of BDP established during the run-in period. If an exacerbation were to occur, after treatment the subject was to return to this baseline dose.

Starting at day 0 and every 4 weeks the following (selected) procedures occurred:

--physical examination
--review and collection of diary cards—data included symptom scores, twice-daily peak expiratory flow, rescue albuterol use, BDP use, and rhinitis symptoms
--spirometry
--filling out asthma exacerbation form

Subjects on the every 2-week schedule required additional clinic visits for injections. They received the following at the intervening visits:

--review and collection of diary cards as above
--spirometry

Comment

The schedule of collection of blood for serum chemistries and hematologies was such that transient laboratory effects, i.e., those of duration less than 16 weeks, would be missed.

Assessment ("core") period, steroid reduction phase, visits 7-13, weeks 16-28

During this period, steroid reduction was to be attempted, with biweekly clinic visits for all subjects and telephone calls. Reduction rules were:

- Every 2 weeks, steroids were to be reduced by approximately 25%.
- If the subject were to worsen, the dose of BDP was to be increased by 25% (or more if deemed necessary by the investigator), and albuterol rescue given. Criteria for worsening

were the same as those defined for the recognition of asthma exacerbations, with the modification that the criterion for worsening of FEV_1 was based on a comparison to the last evaluation prior to the start of steroid reduction (visit 7). The pre-worsening dose of BDP could be instituted after control of asthma symptoms, at the discretion of the investigator.

- Subjects were to remain on the lowest dose of BDP tolerated without one of the above sentinel events for a minimum of 4 weeks prior to the end of the steroid reduction phase.
- Subjects unable to tolerate a steroid reduction were to remain at their baseline BDP dose.

All subjects followed an every-2-week visit schedule (not only those on the every-2-week injection schedule, as in the steroid stabilization period). The same procedures occurred as were performed in the stable steroid period.

In addition, trial personnel were to call subjects every week to monitor health status.

At the end of the period, blood was to be collected for hematology and serum chemistry. A subject and investigator "global" evaluation was to be performed at the end of the period.

Extension period, visits 13-19, weeks 28-52

Immediately following the steroid reduction period, subjects could enter a double-blind extension (although not specified in the protocol, Genentech has stated that subjects were given this as an option, or could discontinue from the trial). Subjects were to be continued on BDP, but treated at an "optimal" dose as determined by the investigator. In addition, although not specified in the protocol, there was to be no restriction on the use of concomitant medications.

During the extension period visits continued every 2 weeks for those subjects on the every-2 week treatment schedule and every 4 weeks otherwise. The interval for the collection of adverse events, performance of interim physical examination, and collection of asthma exacerbation information was relaxed to every 4 weeks (as in the stable steroid phase of the core period).

Follow-up, visit 20, week 64

During the follow-up period, no trial treatment nor rescue medication were administered. At visit 20, asthma exacerbations, adverse events, and concomitant medications were recorded, blood was collected for hematology, serum chemistry, and pharmacokinetics/pharmacodynamics determinations, and spirometry was performed.

Analytical plan

Endpoints

Exacerbations of asthma were the cornerstone of the efficacy evaluation. An asthma exacerbation was defined during the stable steroid and steroid reduction phases as a worsening of asthma requiring treatment with oral or intravenous corticosteroids or a doubling of the inhaled beclomethasone dose from baseline.

The pivotal analysis was performed on asthma exacerbations occurring during the stable steroid and steroid reductions periods of the trial separately; no inferential statistics were performed during the extension phase, when exacerbations were defined slightly differently (a doubling of dose of corticosteroid was defined in the extension in relation to the dose immediately preceding the exacerbation, not in relation to the baseline dose).

Efficacy variables were defined for both the stable steroid and steroid reduction phases of the core period.

- Primary endpoints:
  -- number of exacerbations during the steroid reduction phase
  -- number of exacerbations during the stable steroid phase

- Secondary endpoints:
  During stable steroid phase
  1. number of subject experiencing at least one exacerbation
  2. number of puffs of rescue medication
  During steroid reduction phase
  1. proportion of patients with successful reduction (≥50% dose reduced) of the dose of BDP
  2. proportion of subjects with complete withdrawal of the dose of BDP
  3. percent reduction in the dose of BDP
  4. number of subjects with at least one asthma exacerbation
  5. global evaluation of treatment effectiveness
- Exploratory variables (during stable steroid phase only):
  1. asthma-free days
  An asthma-free day was defined as a day on which all of the following are met:
  -- morning PEFR ≥90% of baseline (mean of the 14 days prior to randomization)
  -- daytime asthma score ≤1
  -- nighttime asthma score =0
  -- rescue medication use ≤2 puffs
  2. morning PEFR
  3. evening PEFR
  4. difference between morning and previous evening PEFR
  5. FEV_1
  6. forced vital capacity, FVC
  7. forced expiratory flow in the middle 50% of expiration, FEF_{25-75}
  8. total asthma symptom score (nocturnal + daytime + morning score)
  9. nocturnal asthma symptom score
  10. presence/absence of morning asthma score
  11. daytime asthma symptom score
- Other variables
  --Change from baseline in adult and pediatric asthma quality of life score (activity limitations, symptoms, emotional function, overall)
  --missed school or work days
  --unscheduled medical contacts

Comments

Endpoints were reasonable in that they were to collect clinically meaningful measures in asthma. Efficacy variables pertaining to corticosteroid reduction were repetitive, measuring slightly different aspects of the same effect. In addition, these reduction variables were to be determined only after a period of use of omalizumab. Physiological variables of greatest interest were FEV_1 and peak flow.

The determination of efficacy during the core period was appropriately separated from the evaluation of asthma exacerbations in the double-blind extension period of the trial, as concomitant medications and corticosteroid use were to be different in the two periods (liberalized in the extension). The determination of efficacy in the extension phase would be expected to be more complicated than that determined under more restrictive conditions. It would more closely resemble conditions of real use, but it would come after a period of use of the investigational agent and a steroid reduction phase immediately preceding it.

Analytical populations

The primary analysis was to be performed on subjects grouped by randomized treatment who had received at least one dose of trial treatment.

Comment

This was not a true intent-to-treat, but since all randomized subjects received at least one dose in either trial, this resulted in a true intent-to-treat analysis.

Sample size

Genentech set the sample size of 550 to achieve sample sizes of 500 after dropouts, which they calculated would give them 92% and 86% power during the steroid reduction and stabilization periods, respectively.

Summary of statistical methods

- Primary endpoint

A stepwise, conditional analysis of the two phases of the core period was to be performed. The steroid reduction phase was to be analyzed first, but only if <10% of subjects dropped out of the trial during the stable steroid phase. If the statistical criterion (p-value of 0.05 on a 2-tailed test) were met for analysis of the steroid reduction phase, the analysis would proceed for the stable steroid phase. If there were >10% dropouts during the stable steroid phase, only the stable steroid phase would be statistically analyzed.

The primary analysis was to be a between-treatment group analysis performed using the Cochran-Mantel-Haenszel (CMH) statistic stratified by treatment schedule using the standardized mid rank to assign weights to the counts. The null hypothesis was to be tested on the mean score location shift. Most of the secondary analyses (except for peak flow and spirometry) were to be performed using the CMH statistic stratified by treatment schedule. Tertiary endpoint analytical techniques were not specified

The primary endpoint analysis included imputations for subjects who discontinued prematurely. The imputation technique was as follows:

  - For subjects who discontinued during a phase, the number of exacerbations attributed to the subject during that phase was the number experienced + the number of days remaining in the period divided by 14. This number was rounded to the nearest integer.
  - For subjects who discontinued during the stable steroid phase, exacerbations were attributed during the steroid reduction phase. The number of exacerbations attributed during the steroid reduction phase was the maximum observed for any subject during the steroid reduction phase + 1.

- Other endpoints

Missing data from diaries (BDP use, peak flows, symptom data) and spirometry data were not to be imputed. The pretreatment average from the last 14 days prior to visit 3 (baseline) was used as the baseline for diary data, except for BDP use, where the pretreatment, visit 3 dose was considered baseline. Visit 3 pretreatment values were baseline for spirometry.

- Interim analysis

There was to be no interim analysis. The efficacy analysis was to be initiated at the completion of the steroid reduction phase, prior to completion of the extension period. The protocol states that the results would be unknown to individuals monitoring the trial.

Comments

The imputation technique for the stabilization phase was a worst-case method that was based on the average duration of asthma exacerbations during Genentech's trial Q0694g (14 days). It represented a highly unlikely series of events, that is, an exacerbation for each 14-day period

remaining in a subject's time in the trial after discontinuation. It would have the effect in the analysis of highly weighting individuals who discontinued early in the trial. The observed maximum number of exacerbations in the stabilization period was about ½ the average of 1 every 2 weeks (it was 3, or an average of 1 every 4 weeks). For further discussion, see CBER's analysis of the primary endpoint.

Unblinding of results during the analysis of the core period had the potential of biasing the conduct of that period. Data on any potential unblinding was not provided in the submission.

Differences between protocols 008 and 009

Trial 009 was nearly identical in design to Trial 008. Minor differences in medications and enrollment criteria were as follows:

- The corticosteroid medication used for control was dispensed in MDIs that delivered 100 μg/puff, not 84 μg/puff as in 008. In addition, the inclusion criterion for stable BDP dosing was stated as 500-1200 μg/day, not 420-840 μg/day as in Trial 008.
- Rescue medication was to be salbutamol (100 μg/puff) instead of albuterol (90 μg/puff). Both medications are acute-acting β-2 agonists.

Protocol modifications

The following changes were made in the one formal protocol amendment, dated May 7, 1998:

- Spirometry and recording of concomitant medications, adverse events, and asthma exacerbations were added at visit 20.
- A clarification was made that the persons preparing or administering the trial agent were not be involved in subject evaluations and added spirometric measurements at visit 20.

Other changes were:
2. After the trials began, it was decided that all subjects, regardless of age, should fill out the adult Juniper quality of life questionnaire (the pediatric questionnaire was originally planned for subjects less than 18 years old). However, 8 subjects in trial 008 and 25 subjects in trial 009 who had started with the pediatric questionnaire were asked to continue with the pediatric version. In addition, because of the manner in which some subjects filled out a component of the questionnaire, the primary analysis of questionnaire data was modified.

3. A site was closed with transfer of subjects to another site in the same city. Genentech states: "In July 1999, USA site 2153 was closed because the principal investigator, Dr. Grossman, was no longer working there. Any patients remaining in the study at that time were transferred to the care of Dr. LaHood, at a different site in the same city. The center number remained as 2153."

Comments

The trials had an adequate duration and collected clinically meaningful data. They were sized to measure two aspects of the product's effect: reduction in asthma exacerbation incidence, and the effect on corticosteroid dosing. The protocols made no effort to collect information on subjects selected for high degrees of severity or those on commonly used concomitant medications in asthma. Changes made to the protocols after they were implemented would be expected to have no appreciable impact on the overall evaluation of efficacy.

Results: Conduct of the trial

Dates of the trials

The first subject was recruited into trial 008 on February 9, 1998, and the last subject completed the trial on January 19, 2000. The first subject was recruited into trial 009 on April 26, 1998, and the last subject completed the trial on May 24, 2000.

Screening failures

Just over twice as many subjects were screened as entered into trial 008: 1117 vs. 525. The major reasons for failing to be entered into the trial were: FEV_1 over 80% predicted (152 persons, 14%) and serum IgE>700 (101 persons, 9%). Notably, 53 (4.7%) were screened out for IgE below the treatment limit, and 36 (3.2%) were screened out for having a combination of IgE and body mass outside the dosing table limits.

Out of 1356 subjects screened for trial 009, 810 failed to meet selection criteria. The major reasons for failing to be entered into trial 009 were serum IgE>700 (162 persons, 12%) and FEV_1 over 80% predicted (161 persons, 12%). Notably, 71 (4.7%) were screened out for IgE below the treatment limit, and 21 (1.5%) were screened out for having a combination of IgE and body mass outside the dosing table limits.

Comments

A substantial proportion of subjects were screened out of both of these trials due to serum IgE levels or FEV_1 higher than the limit for the trials; a smaller, and notable numbers were screened out due to IgE levels lower than the protocol limit. These IgE-related exclusions are important because of the potential variability in serum IgE. In clinical practice, patients might be tested at multiple times, and qualify on the basis of one of many determinations.

Enrollment by site

Trial 008

There were 26 sites in trial 008 (Table 15). No single site dominated the enrollment in this trial. The largest enrollment for a given site was 29, the smallest, 5, with enrollment well distributed in between. Sixteen sites had greater than 20 subjects; 4 had fewer than 10. For the purposes of analysis, Genentech pooled sites 3 and 8.

Table 15. Trial 008: Enrollment by site

Number of subjects/site	Number of sites
5-8	4
11-19	6
22-25	10
27-29	6

Trial 009

There were 42 sites in trial 009 (Table 16). The largest enrollment was 41, the smallest, 1. In contrast to trial 008, enrollment tended to be smaller at each site, with 16 sites enrolling 10 subjects or less. Nine sites had enrollment over 20.

Table 16. Trial 009: Enrollment by site

Number of subjects /site	Number of sites
1-4	7
5-10	14
11-16	10
21-25	7
27-32	3
41	1

Comment

Site enrollment was not dominated by any one center in either trial.

Demographics and baseline characteristics

Trial 008

Table 17 shows that in trial 008 the placebo and omalizumab groups were well matched for important baseline characteristics and demographics. There were about 1½ times as many females as males in the trial (but the proportions were approximately equal in trial 009). The trial population was primarily Caucasian. The trial was primarily adult, with 7-8% adolescents. Investigators uniformly answered the question about whether subjects were going to be exposed to a relevant allergen in the affirmative.

Genentech prospectively defined two classifications for asthma: those whose FEV_1 percent predicted at visit 3 was ≤65% and who had an average symptom score during the 14 days prior to visit 3 that was >4, and all others. Using this stratification, the two treatment arms were well matched (22% in the more severe category in the omalizumab group vs. 21% in the more severe category in the placebo group).

Table 17. Trial 008: Demographics and baseline characteristics

	Omalizumab N=268	Placebo N=257
Sex, N (%) Male Female	 104 (38.8) 164 (61.2)	 111 (43.2) 146 (56.8)
Race, N (%) Caucasian Black Other	 238 (88.8) 21 (7.8) 9 (3.4)	 229 (89.1) 16 (6.2) 12 (4.7)
Age group, N (%) 12 - 17 years 18 - 64 years ≥65 years	 20 (7.5) 241 (89.9) 7 (2.6)	 21 (8.2) 229(89.1) 7 (2.7)
Mean Age, year (range)	39.3 (12-73)	39 (12-74)
Mean duration of asthma, year (range)	20.56 (1 – 61)	22.65 (2 – 60)
Smoking status (n, %) Never smoked Ex-smoker	 204 (76.1) 64 (23.9)	 181 (70.4) 76 (29.6)
BDP dose at baseline visit, mcg/day (range)	570 (420 – 1008)	568 (336 – 840)
Mean serum total IgE, IU/ml (range)	172 (20 – 860)	186 (21 – 702)
Mean serum total IgE, IU/ml by treatment schedule	Q2w: 292 Q4w: 95	Q2w: 314 Q4w: 103
Mean FEV_1, % predicted (range)	68.2 (30 – 112)	67.7 (32 – 111)
Mean qualifying FEV_1 reversibility, (%)	26.9	25.9
Subjects with hospitalization for asthma treatment past year, N (%)	6 (2)	11 (4)
Mean number of emergency room visits for asthma past year	0.2	0.3
Mean number of doctor's office visits for urgent asthma treatment past year	0.7	0.8

Trial 009

Table 18 shows that in trial 009 the placebo and omalizumab groups were also well matched for important baseline characteristics and demographics. In contrast to trial 008, the proportions of each gender enrolled was nearly matched. The proportion of Caucasians and adults (the large majorities) was similar to that of trial 008. Investigators uniformly answered the question about whether subjects were going to be exposed to a relevant allergen in the affirmative.

Using the stratification of severity described for trial 008 the two treatment arms were well matched and very similar to those in trial 008 (22% in the more severe category in both treatment arms).

Table 18. Trial 009: Demographic and baseline characteristics

	Omalizumab *n=274*	Placebo *n=272*
Sex n(%)		
male	141 (51.5)	127 (46.7)
female	133 (48.5)	145 (53.3)
Race n(%)		
Caucasian	256 (93.4)	242 (89.0)
Black	11 (4.0)	11 (4.0)
Oriental	2 (0.7)	6 (2.2)
Other	5 (1.8)	13 (4.8)
Age n(%)		
12-17years	18 (6.6)	17 (6.3)
18-64years	237 (86.5)	246 (90.4)
≥65years	19 (6.9)	9 (3.3)
Age (years)		
mean (range)	40.0 (12-76)	39.0 (12-72)
Duration of asthma (yrs.)		
mean (range)	20.3 (2-68)	19.1 (1-63)
Smoking status [n(%)]		
non-smoker	213 (77.7)	207 (76.1)
ex-smoker	61 (22.3)	65 (23.9)
BDP dose (µg/day)		
mean (range)	769 (500-1600)	772 (200-2000)
Mean serum total IgE, IU/ml	Q2w: 358	Q2w: 338
by treatment schedule	Q4w: 107	Q4w: 98
% predicted FEV_1		
mean (range)	69.8 (30-112)	69.9 (22-109)
Qualifying FEV_1 reversibility (%)		
Mean (range)	26.4 (10-86)	25.8 (11-103)
Past year hospital or doctor visits for asthma:		
Subjects with overnight hospital admission n (%)	11 (4.1)	20 (7.5)
Mean number of emergency room visits (range)	0.23 (0-12)	0.17 (0-6)
Mean number of doctor's office visits (range)	1.18 (0-15)	1.21 (0-24)
Mean number of missed work or school days (range)	4.34 (0-190)	2.82 (0-60)

Comments

Trials 008 and 009 enrolled a primarily adult Caucasian population of asthmatics of whom very few were in the geriatric age range.

The proportions of subjects with hospital admissions and emergency room visits was low. In addition, subjects in this trial were able to be managed solely with inhaled corticosteroid, not requiring oral (ingested) corticosteroids, without other asthma medications. Subjects whose asthma is difficult to control were not studied in these trials.

Demographic and baseline characteristics were well matched.

Premature discontinuations

[This reviewer is indebted to Dr. Dwaine Rieves, CBER for the organization of data as presented in Table 19 and Table 20.]

Trial 008

Table 19 shows the numbers of subjects who completed trial 008, and the reasons for dropping out. Reasons for failure to complete the core period were fairly balanced, with the exception of "unsatisfactory therapeutic effect," which was cited as a reason in noticeably more placebo subjects than omalizumab subjects. Withdrawal of consent was the most frequent reason for premature discontinuation during the core period, occurring somewhat more frequently in placebo (7 active, 11 placebo); reasons cited were similar for both groups. Administrative problems predominated reasons for failure to complete the extension period.

Although not directly pertinent to the evaluation of efficacy, it should be noted that more subjects completed their follow-up examination than completed the extension phase. This was due to the fact that early discontinuers were instructed to have a follow-up examination.

Table 19. Trial 008: Subject disposition [*n* (%)]

Total no. patients, n (%)	Omalizumab	Placebo
Double blind 7 months core period		
Randomized	268	257
Competed stabilization	255 (95%)	234 (91%)
Completed steroid reduction	249 (93%)	223 (87%)
Discontinued	19 (7.1%)	34 (13.2%)
due to death	0	1 (0.4%)
due to AE	2 (0.7%)	2 (0.8%)
due to unsatisfactory therapy	1 (0.4%)	14 (5.4%)
due to protocol violation	1 (0.4%)	0
due to consent withdrawal	7 (2.6%)	11 (4.3%)
due to administrative problem	4 (1.5%)	2 (0.8%)
lost to follow-up	4 (1.5%)	4 (1.6%)
Double blind 5 month extension period		
Completed core study but did not enter extension study	4 (1.5%)	8 (3.1%)
Enrolled in extension	245 (91.4%)	215 (83.7%)
Completed extension	233 (86.9%)	207 (80.5%)
Discontinued	12 (4.5%)	8 (3.1%)
due to administrative problem	8 (3.0%)	1 (0.4%)
due to consent withdrawal	1 (0.4%)	5 (1.9%)
due to unsatisfactory therapy	1 (0.4%)	1 (0.4%)
lost to follow-up	2 (0.7%)	1 (0.4%)
Three month no treatment follow-up period		
Completed extension and completed follow-up period	231 (86.1%)	203 (79.0%)
Discontinued from extension study but completed follow-up period	4 (0.1%)	5 (0.2%)
Completed core study, did not enter extension but completed follow-up period	3 (0.1%)	6 (0.2%)
Discontinued from core study but completed follow-up period	3 (0.1%)	15 (5.9%)
Lost to follow-up	27 (10%)	28 (10.8%)

Trial 009

Table 20 shows the numbers of subjects who completed trial 009. As in trial 008, more placebo subjects discontinued. More placebo subjects discontinued for lack of therapeutic effect as in 008, but the discrepancy between placebo and omalizumab was not as great. Reasons for withdrawal of consent were primarily not illness-related.

As in trial 08, more subjects completed their follow-up examination than completed the extension phase: 22 active and 37 placebo subjects did not complete the follow-up examination.

Table 20. Trial 009: Subject disposition [*n*(%)]

Total no. patients, n (%)	Omalizumab	Placebo
Double blind 7 months core period		
Randomized	274	272
Competed stabilization	261 (95.3%)	245 (90.1)
Completed steroid reduction	255 (93.1%)	232 (85.3%)
Discontinued	19 (6.9%)	40 (14.7%)
due to death	0	0
due to AE	0	5 (1.8%)
due to unsatisfactory therapy	3 (1.1%)	8 (2.9%)
due to protocol violation	5 (1.8%)	6 (2.2%)
due to consent withdrawal	3 (1.1%)	14 (5.1%)
due to administrative problem	1 (0.4%)	4 (1.5%)
due to abnormal lab value	1 (0.4%)	0
lost to follow-up	6 (2.2%)	3 (1.1%)
Double blind 5 month extension period		
Completed core study but did not enter extension study	1 (0.4%)	3 (1.1%)
Entered into extension	254 (92.7%)	229 (84.2%)
Completed extension	244 (89.1%)	203 (74.6%)
Discontinued	10 (3.6%)	26 (9.6%)
due to adverse event	2 (0.7%)	3 (1.1%)
due to abnormal lab value	1 (0.4%)	1 (0.4%)
due to unsatisfactory therapy	0	3 (1.1%)
due to consent withdrawal	4 (1.5%)	12 (4.4%)
due to lost to follow-up	2 (0.7%)	7 (2.6%)
due to protocol violation	1 (0.4%)	0
Provided any follow-up data	252 (92.0%)	235 (86.4%)
Three month no treatment follow-up period		
Completed extension and completed follow-up period	243 (88.7%)	200 (73.5%)
Discontinued from extension period but completed follow-up period	4 (1.5%)	16 (5.9%)
Completed core period, did not enter extension but completed follow-up period	1 (0.4%)	2 (0.7%)
Discontinued from core period but completed follow-up period	4 (1.5%)	17 (6.3%)
No final follow-up visit	22 (8.0%)	37 (13.6%)

Comments

The proportion of discontinuations in the placebo arm during the stable steroid phase of each trial was close to 10%, and a further 4-5% during the steroid reduction phase; corresponding reductions in the omalizumab group were around 5% and 2%. These two factors, the imbalance of the proportions of discontinuations and the relatively large proportion of these subjects to the total in each treatment arm, created a noticable difference in the magnitude of the treatment effect as analyzed by the protocol-defined technique and by other techniques (see analysis of efficacy results).

Dropouts during the extension phase, whose efficacy results will be reviewed in a separate section from the stable steroid and steroid reduction primary analyses, occurred at about a further 3-4% rate for each treatment arm during trial 008, but were noticeably imbalanced during trial 009 (rates of about 3-4% in the omalizumab arm and 10-11% in the placebo arm). The efficacy evaluations during this phase of the trial were not considered primary.

Eligibility, dosing, and other protocol violations

Table 21 and Table 22 show frequent and important protocol violations for the core and extension periods of trials 008 and 009. Violations were summarized separately for the core and extension periods of trial 009; some of the subjects may have been the same as in the core period, potentially leading to redundancy in the table. However, the numbers of violations in the extension period was small, so the error would not be great.

Table 21. Trial 008: Most common protocol violations during core and extension periods (proportion of subjects affected per group*)

Violation	Omalizumab *N=268*	Placebo *N=257*
Run-in period <4 weeks	45 (17)	49 (19)
Beta agonist <6 hours before spirometry	32**	64**
Excluded concomitant med**	22	30
Run in period stable BDP dose 3 to <4 weeks	15 (5.6)	15 (5.8)
Reduced BDP dose in last 4 weeks of reduction phase	14 (5.2)	13 (5.1)
Baseline serum IgE <30	18 (6.7)	7 (2.7)
Dosing error (missed or extra dose)	7**	16**
Baseline mean symptom score <3	10 (3.7)	15 (5.8)
IgE/weight out of dosing table range	7 (2.6)	3 (1.2)
FEV_1 % >80%	6 (2.2)	2 (0.8)

* Protocol violations not listed by subject in submission; calculated by CBER when likely to be single occurrence; proportions expressed as proportions of enrolled population

**possible multiple occurrences; incidence by subject not calculated by CBER

Table 22. Trial 009: Most common protocol violations during core and extension periods (proportion of subjects affected per group)

Period	Violation	Omalizumab	Placebo
Core		*N=274*	*N=272*
	Run-in period stable BDP dose 3 to <4 weeks	75 (27)	75 (28)
	Beta agonist <4 hours before spirometry	58 (17)	104 (26)
	Run-in period <4 weeks	39 (14)	33 (12)
	Baseline mean symptom score <3	46 (17)	39 (14)
	IgE/body weight outside dosing table range and dosing ≥0.007 mg/kg/IU/ml Q2w	23 (8.4)	23 (8.5)
	Excluded concomitant medication	14 (4.7)	22 (6.3)
	FEV_1% >80%	12 (4.4)	5 (1.8)
	Reduced BDP dose in last 4 weeks of reduction phase	5 (1.8)	9 (3.3)
	FEV_1% <40%	11 (4.0)	1 (0.4)
Extension		*N=254*	*N=229*
	Beta agonist <4 hours before spirometry	12 (5)	6 (3)
	Missing or additional dose	3 (1)	1 (0.4)

- For both trials, run-in period duration violations were relatively frequent but were balanced between arms.
- Rescue medication violations prior to spirometry were not well balanced and might have affected FEV_1, a secondary endpoint, biasing against the product.
- Unstable doses of corticosteroid at the beginning of the trial would be expected to create more variability in the corticosteroid endpoint of the trial; the number of these violations was balanced.
- Reductions in corticosteroid dosing too close to the end of the steroid reduction phase were infrequent and approximately equal in occurrence in the two treatment arms.
- Excluded concomitant medications violations were infrequent and reasonably balanced.
- FEV_1 criteria violations in trial 009 were unbalanced, but relatively infrequent, and occurred in opposite directions in a balanced way.

- Genentech expressed dosing violations for mean dose as numbers of subjects with mean dose less than 0.008 mg/kg/IU/ml every 2 weeks. For trial 008, 5 active-treated subjects and 0 placebo subjects fell into this category; for trial 009, 1 subject in each treatment arm fell into this category.

Comments

Violations of run-in periods were the most common protocol violation in both trials. A too-brief run-in period could potentially have introduced uncertainty in the corticosteroid dosing at the start of the steroid stabilization period. The most problematic outcome of this would be to introduce variability in efficacy measures, but the effect would likely be equal since the violation was equally distributed between treatment arms and was in the same direction (too short a period for both arms). Thus this frequent violation would not have been expected to have an impact in the assessment of efficacy. Other violations with potential impact on the efficacy results of the trials were uncommon, so the impact on the overall results would have been expected to be small. Overall, protocol violations were unlikely to have affected the assessment of efficacy in either trial.

Data base issues

- *Changes to the data base after data lock*

Trial 008

Genentech notes that after data base lock, for 1 omalizumab-treated and 4 placebo-treated subjects, the numbers of exacerbations (even if imputed) was noted to have been undercounted by 1. The data base was not changed to correct this undercount. This undercount is unlikely to have any impact on the results of the trial.

Trial 009

Following the lock of the core data base on October 25, 1999, further core data were received by the data management group for trial 009. The BLA submission states that the data base was unlocked 3 times to make changes:

1. 6 concomitant medication records that had not been coded against the International Therapeutic Dictionary were coded.
2. a. 4 asthma exacerbations (3 protocol-defined, 1 in active-, and 2 in placebo-treated subjects) were added to the data base.
   b. 4 protocol violations were added (1 active subject, 2 placebo subjects).
3. Errors in the laboratory data were corrected.

Efficacy analyses were performed after data base change 2.

- *Transcription of medication data pertaining to exacerbations*

Genentech notes that some data relating to asthma exacerbations was not encoded on asthma exacerbation forms by investigators. For trial 008, full data on medications was recorded on the asthma exacerbation form for 95.2% and 92.7% of records in the omalizumab and placebo groups, respectively; for trial 009, 84.5% and 92.0%, respectively). The data cleanup procedures resulted in transfer of medication data from concomitant medication and diary sections to asthma exacerbation forms. Upon request, detailed listings of the origin of medication information, as well as case report form pages, were supplied to the BLA. Review of the data submitted upon request by Genentech does not show an irregularity in the correction of asthma exacerbation medication data for either trial.

- *Transcription of exacerbation classification data*

CBER compared data tabulations with classifications of exacerbations as represented in the case report forms of 32 subjects in trial 008 and 29 subjects in trial 009 (about 47 records of

exacerbations in trial 008 and 33 in trial 009). The forms were examined for events in the core period for trial 008; phase information was not encoded in the forms for trial 009, and this review does not draw this distinction. Errors in which exacerbations were encoded in the data tabulations as protocol-defined but the reason was not apparent from examination of case report forms, or when a protocol-defined event was apparently missed, were rare (in trial 008, 2 possible misrepresented cases, both in omalizumab subjects, and in opposite directions; in trial 009, 2 possible misattributions of a protocol-defined event to placebo subjects).

Comments

Genentech supplied further information upon request detailing changes that were made to the data base after data base lock. For trial 008, the response indicated that three minor changes were made to the asthma exacerbation records, which would not be expected to have an impact on the efficacy results of the trial. For trial 009, additional information such as associated adverse events or medications was supplied on 12 asthma exacerbations; in 2 instances, both in a placebo subjects, a question relating to a protocol-defining event was changed (from "no" to "yes"). In addition, 3 asthma exacerbations were discovered that were not added to the data base (1 protocol-defined, 2 nonprotocol-defined. These changes would not be expected to have changed the analysis of the trial significantly.

The changes and potential errors noted with regards to exacerbation classification coding would be expected to have a negligible effect on the overall conclusions regarding efficacy in the trials.

Exposure to product

Trial 008

Table 23 shows the duration of exposure to trial agent in all randomized subjects. Genentech states that in the group whose exposure was greater than the nominal 28 weeks +3 days, there were 86 (32%) in the omalizumab-treated group whose exposure was 200-225 days and 77 (30%) in the placebo-treated group whose exposure was 200-253 days, all accounted for by an increase in time during the core period, and not an increase in the number of injections (see protocol violations table above for information on missed or extra doses).

Table 23. Duration of exposure to omalizumab or placebo in all randomized subjects: Numbers and proportions of subject per group

	008		009	
Weeks	Omalizumab *N=268*	Placebo *N=257*	Omalizumab *N=274*	Placebo *N=272*
0 - <1	1 (0.4)	4 (1.6)	3 (1.1)	6 (2.2)
1 - <4	1 (0.4)	3 (1.2)	1 (0.4)	2 (0.7)
4 - <8	4 (1.5)	3 (1.2)	1 (0.4)	4 (1.5)
8 - <12	2 (0.7)	6 (2.3)	3 (1.1)	11 (4.0)
12 -<16	5 (1.9)	6 (2.3)	6 (2.2)	5 (1.8)
16 -<20	5 (1.9)	7 (2.7)	1 (0.4)	7 (2.6)
20 - <24	0 (0.0)	4 (1.6)	2 (0.7)	1 (0.4)
24 - <28	32 (11.9)	30 (11.7)	29 (10.6)	23 (8.5)
28 - <32	216 (80.6)	190 (73.9)	220 (80.3)	208 (76.5)
32 - <36	2 (0.7)	3 (1.2)	8 (2.9)	5 (1.8)
36- <40	0 (0.0)	1 (0.4)	-	-

Differences between the groups in duration of exposure were affected by the larger number of dropouts in the placebo group (see Table 19 and Table 20). Aside from this, compliance to trial agent administration according to protocol requirements appears to have been very good.

Completeness of data collection

CBER examined diary and spirometry data (symptoms, medication usage, and FEV_1 and FVC respectively) files. For diary data, the submission included raw data for the core period only (not the extension or follow-up periods). Raw spirometry data were included for the core, extension, and follow-up periods. As a proportion of diary entries for the core period, missing diary data averaged between 5-6% in trial 008 and between 3-4% in trial 009; spirometry, which was conducted by trial personnel, was better; missing FEV_1 and FVC data in trial 008 was 0.6% and 2%, respectively, and for trial 009, 0.5% and 1%, respectively. Exacerbation data were collected on forms filled out when an event occurred, and not on a fixed schedule, rendering completeness of collection of these data difficult to assess.

Data collection was very good in trials 008 and 009.

Comment

In summary, the conduct of the trial was good, and allows justifiable conclusions from a review of efficacy data as presented.

Results: Efficacy

Primary endpoint

The primary analytical population for these trials was all randomized subjects who received trial medication. Since all subjects received at least one injection, this was equivalent to an intent-to-treat population.

As noted above in the section "data base issues" the submitted analyses do not include several protocol-defined exacerbations that were determined after unblinding to have been left out of the data base. The statistical method for the primary analysis was summarized in the outline of the protocol above.

Primary endpoint: asthma exacerbations during stable steroid phase

Trial 008

Table 24 shows exacerbations as determined in trial 008 using the protocol-defined technique of imputation. The CMH test stratified by dosing frequency favored omalizumab with a p-value of 0.006.

Table 24. Trial 008: Asthma exacerbations in stable steroid phase (subjects, %)*

	Q2w dosing		Q4w dosing		Overall	
Number of exacerbations	Omlzmb *n=106*	Placebo *n=101*	Omlzmb *n=162*	Placebo *n=156*	Omlzmb *n=268*	Placebo *n=257*
0	87 *82%*	75 *74%*	142 *88%*	122 *78%*	229 *85%*	197 *77%*
1	11 *10%*	9 *9%*	16 *10%*	23 *15%*	27 *10%*	32 *13%*
>1	8 *8%*	17 *17%*	4 *2%*	11 *7%*	12 *4%*	28 *11%*
total ≥1	19 *18%*	26 *26%*	20 *12%*	34 *22%*	39 *15%*	60 *23%*

*ITT population; imputation according to protocol

Trial 009

Table 25 shows exacerbations as determined in trial 009 using the protocol-defined technique of imputation. The CMH test stratified by dosing frequency favored omalizumab with a p-value of <0.001.

Table 25. Trial 009: Asthma exacerbations in stable steroid phase (subjects, %)*

Number of exacerbations	Q2w dosing		Q4w dosing		Overall	
	Omlzmb *n=127*	Placebo *n=122*	Omlzmb *n=147*	Placebo *n=150*	Omlzmb *n=274*	Placebo *n=272*
0	112 *88%*	87 *71%*	127 *86%*	102 *68%*	239 *87%*	189 *69%*
1	9 *7%*	19 *16%*	16 *11%*	30 *20%*	25 *9%*	49 *18%*
>1	6 *5%*	16 *13%*	4 *3%*	18 *12%*	10 *4%*	34 *13%*
total ≥1	15 *12%*	35 *29%*	20 *14%*	48 *32%*	35 *13%*	83 *31%*

*ITT population; imputation according to protocol

Comments

Most subjects in both groups in both trials experienced no exacerbations (see also comment under the review of different imputation analyses), so the treatment effect was seen in a relatively small number of subjects. There was a greater placebo rate of exacerbations in trial 009, leading to a greater treatment effect. Omalizumab was effective in reducing the numbers of subjects with exacerbations in both treatment schedules.

Primary endpoint: asthma exacerbations during steroid reduction phase

Trial 008

Table 26 shows exacerbations as counted using the protocol-defined technique of imputation. The CMH test stratified by dosing frequency favored omalizumab with a p-value of 0.003.

Table 26. Trial 008: Asthma exacerbations in steroid reduction phase (subjects, %)*

Number of exacerbations	Q2w dosing		Q4w dosing		overall	
	Omlzmb *n=106*	Placebo *n=101*	Omlzmb *n=162*	Placebo *n=156*	Omlzmb *n=268*	Placebo *n=257*
0	85 *80%*	58 *57%*	126 *78%*	116 *74%*	211 *79%*	174 *68%*
1	9 *9%*	23 *23%*	25 *15%*	17 *11%*	34 *13%*	40 *16%*
>1	12 *11%*	20 *20%*	11 *7%*	23 *15%*	23 *9%*	43 *17%*
total ≥1	21 *20%*	43 *43%*	36 *22%*	40 *26%*	57 *21%*	83 *32%*

*ITT population; imputation according to protocol

Trial 009

Table 27 shows exacerbations as counted using the protocol-defined technique of imputation. The CMH test stratified by dosing frequency favored omalizumab with a p-value of <0.001.

Table 27. Trial 009: Asthma exacerbations in steroid reduction phase (subjects, %)*

Number of exacerbations	Q2w dosing		Q4w dosing		overall	
	Omlzmb *n=127*	Placebo *n=122*	Omlzmb *n=147*	Placebo *n=150*	Omlzmb *n=274*	Placebo *n=272*
0	109 *86%*	86 *71%*	122 *83%*	105 *70%*	231 *84%*	191 *70%*
1	7 *6%*	14 *12%*	14 *10%*	21 *14%*	21 *8%*	35 *13%*
>1	11 *9%*	22 *18%*	11 *7%*	24 *16%*	22 *8%*	46 *17%*
total ≥1	18 *14%*	36 *30%*	25 *17%*	45 *30%*	43 *16%*	81 *30%*

*ITT population; imputation according to protocol

Comments

The proportions of subjects experiencing exacerbations during the steroid reduction phase in trial 008 were nearly equal in the Q4w group (slightly favoring omalizumab), but favored omalizumab much more strongly in the Q2w group. (This difference in effect between the treatment schedules in trial 008 was detected in a statistical analysis by Genentech of the numbers of subjects ³1 exacerbation: The Breslow-Day test of subjects with any number of exacerbations showed a difference with a p-value of 0.026 between the treatment schedules in trial 008.) This occurred due to the larger proportion of omalizumab-treated subjects with 1 exacerbation exactly in the Q2w group (while a smaller proportion had ³1 exacerbation). However, in trial 009 omalizumab was clearly associated in the primary analysis with a more favorable outcome in both treatment schedules. Because the lack of difference was not replicated in trial 009, nor in either trial in the stable steroid phase, it can be viewed as an isolated event, and does not change substantially the overall assessment of efficacy for either treatment schedule. The treatment was effective in both trials considering both treatment schedules together or separately.

Submitted sensitivity analyses of primary endpoint

- *Analysis of observed exacerbations and analysis using 3 different imputation techniques*

Genentech analyzed protocol-defined exacerbations on the intent-to-treat population in trials 008 and 009 using 3 imputation techniques different from the primary analysis. The methods are summarized as follows:

1. Observed exacerbations: This method uses observed exacerbations only.
2. Single exacerbation imputation: This assigns 1 exacerbation to the subjects who discontinue (not an additional one), and 1 during the reduction period for those who discontinue during the stable steroid period.
3. Maximum observed exacerbation imputation: This assigns the maximum number of observed exacerbations (for both groups) for that period, including for those who discontinue in the stable steroid period.

The statistical method was the same as the primary analysis.

This review will show detailed results from analysis using observed exacerbations, then will show a comparison of results using the protocol-defined method of imputation and the 3 additional methods.

Detailed analysis of observed exacerbations

Most subjects did not have any exacerbations. For this reason, analysis of observed exacerbations mirrors more closely the behavior of the trial population, and is conservative in this case because of the greater number of discontinuations in the placebo group. This section will show observed exacerbation counts for comparison to the exacerbation counts presented in the primary analysis.

Stable steroid phase

Trial 008

Table 28 shows observed protocol-defined asthma exacerbations for the stable steroid phase of trial 008. Using the same statistical method as for the primary analysis, the p-value is 0.026.

Table 28. Trial 008: Asthma exacerbations in stable steroid phase, observed (subjects, %)*

	Q2w dosing		Q4w dosing		Overall	
Number of exacerbations	Omalizumab *n=106*	Placebo *n=101*	Omalizumab *n=162*	Placebo *n=156*	Omalizumab *n=268*	Placebo *n=257*
0	93 *88%*	83 *82%*	145 *90%*	127 *81%*	238 *89%*	210 *82%*
1	11 *10%*	11 *11%*	15 *9%*	25 *16%*	26 *10%*	36 *14%*
>1	2 *2%*	7 *7%*	2 *1%*	4 *3%*	4 *1%*	11 *4%*
total ≥1	13 *12%*	18 *18%*	17 *10%*	29 *19%*	30 *11%*	47 *18%*

*ITT population

Trial 009

Table 29 shows observed protocol-defined asthma exacerbations for the stable steroid phase of trial 009. Using the same statistical method as for the primary analysis, the p-value is <0.001.

Table 29. Trial 009: Asthma exacerbations in stable steroid phase, observed (subjects, %)*

	Q2w dosing		Q4w dosing		Overall	
Number of exacerbations	Omalizumab *n=127*	Placebo *n=122*	Omalizumab *n=147*	Placebo *n=150*	Omalizumab *n=274*	Placebo *n=272*
0	118 *93%*	98 *80%*	129 *88%*	111 *74%*	247 *90%*	209 *77%*
1	9 *7%*	20 *16%*	16 *11%*	32 *21%*	25 *9%*	52 *19%*
>1	0	4	2	7	2	11
	0%	*3%*	*1%*	*5%*	*1%*	*4%*
total ≥1	9 *7%*	24 *20%*	18 *12%*	39 *26%*	27 *10%*	63 *23%*

*ITT population

Steroid reduction phase

Trial 008

Table 30 shows observed protocol-defined asthma exacerbations for the steroid reduction phase of trial 008. Using the same statistical method as for the primary analysis, the p-value is 0.124.

Table 30. Trial 008: Asthma exacerbations in steroid reduction phase, observed (subjects, %)*

	Q2w dosing		Q4w dosing		Overall	
Number of exacerbations	Omalizumab *n=106*	Placebo *n=101*	Omalizumab *n=162*	Placebo *n=156*	Omalizumab *n=268*	Placebo *n=257*
0	95 *90%*	74 *73%*	134 *83%*	132 *85%*	229 *85%*	206 *80%*
1	9 *8%*	24 *24%*	25 *15%*	18 *12%*	34 *13%*	42 *16%*
>1	2 *2%*	3 *3%*	3 *3%*	6 *4%*	5 *2%*	9 *4%*
total ≥1	11 *10%*	27 *27%*	28 *17%*	24 *15%*	39 *15%*	51 *20%*

**ITT population

Trial 009

Table 27 shows observed protocol-defined asthma exacerbations for the steroid reduction phase of trial 009. Using the same statistical method as for the primary analysis, the p-value is 0.022.

Table 31. Trial 009: Asthma exacerbations in steroid reduction phase, observed (subjects, %)*

	Q2w dosing		Q4w dosing		Overall	
Number of exacerbations	Omalizumab *n=127*	Placebo *n=122*	Omalizumab *n=147*	Placebo *n=150*	Omalizumab *n=274*	Placebo *n=272*
0	119 *94%*	104 *85%*	129 *88%*	124 *83%*	248 *91%*	228 *84%*
1	7 *6%*	14 *11%*	14 *10%*	22 *15%*	21 *8%*	36 *13%*
>1	1 *1%*	4 *3%*	4 *3%*	4 *3%*	5 *2%*	8 *3%*
total ≥1	8 *6%*	18 *15%*	18 *12%*	26 *17%*	26 *9%*	44 *16%*

**ITT population

Comment

The magnitude of the treatment effects was slightly smaller using the observed counts, but the treatment effect was preserved. The statistical results are shown in the following section.

Summary of different imputation analyses

Table 32 shows the results of the statistical test described on the various defined populations, and displays mean exacerbation counts for each method and phase. These results were confirmed by the CBER statistician, with the exception of the p-value during the stable steroid phase of trial 008, which CBER calculated as 0.018 for the observed count method.

Table 32. Trials 008 and 009: Mean exacerbations per subject and p-value using different imputation techniques

Trial	Imputation Method	Stable steroid phase			Steroid reduction phase		
		Omlzmb	Placebo	*p-value*	Omlzmb	Placebo	*p-value*
008	Protocol	0.28	0.54	*0.006*	0.39	0.66	*0.003*
	Observed (no imputations)	0.13	0.23	*0.026*	0.16	0.23	*0.124*
	Single	0.17	0.27	*0.012*	0.23	0.36	*0.004*
	Maximum	0.26	0.45	*0.011*	0.3	0.49	*0.003*
009	Protocol	0.28	0.66	*<0.001*	0.36	0.75	*<0.001*
	Observed (no imputations)	0.11	0.29	*<0.001*	0.12	0.2	*0.022*
	Single	0.15	0.36	*<0.001*	0.19	0.34	*<0.001*
	Maximum	0.24	0.56	*<0.001*	0.32	0.63	*<0.001*

Comments

As noted before, the number of exacerbations in these trials was small; the median number of exacerbations using any method of imputation was 0.

Alternative imputation techniques, and no imputation, resulted in a decrease in effect size in both trials, but the results all favored omalizumab and nearly all analyses still showed a difference that was statistically significant. The importance of the early discontinuations and the imputation applied to them is illustrated most clearly by the large difference within each group between the protocol-specified imputation and the observed-only methods.

- *Analysis of intensity of steroids used for exacerbations*

Trial 008

Upon request, Genentech performed an analysis of the intensity of corticosteroid treatment administered for observed asthma exacerbations for both the stable and reduction phases (Table 33). This analysis is an alternative method of determining the intensity of the exacerbation. The use of IV corticosteroids would be expected in the most severe exacerbations; oral use would be next most intense treatment provided, and a doubling of inhaled corticosteroid only would be expected to be recommended for the least severe protocol-defined asthma exacerbations. In this analysis, exacerbations are counted only once, for the most intense corticosteroid used.

Table 33. Observed exacerbations (n, %) by maximum intensity of corticosteroids used in treatment

Trial	Most intensive corticosteroid used	Stable steroid phase		Steroid reduction phase	
		Omlzmb	Placebo	Omlzmb	Placebo
008	Doubling of inhaled	7 *20%*	12 *20%*	4 *9%*	5 *8%*
	Oral	28 *80%*	45 *76%*	39 *89%*	55 *92%*
	IV	0 *0%*	2 *3%*	1 *2%*	0 *0%*
	TOTAL	35 *100%*	59 *100%*	44 *100%*	60 *100%*
009	Doubling of inhaled	5 18%	18 *23%*	1 *3%*	9 *17%*
	Oral	23 82%	54 *69%*	29 *94%*	41 *76%*
	IV	0 0%	6 *8%*	1 *3%*	4 *7%*
	TOTAL	28 *100%*	78 *100%*	31 *100%*	54 *100%*

Comments

Table 33 shows that there were very few asthma exacerbations in either treatment arm severe enough to require intravenous corticosteroid administration. Most of the asthma exacerbations were qualified as protocol-defined exacerbations because of the administration of oral corticosteroids, and few due to the relatively moderate step of doubling inhaled corticosteroids. The data show that the reduction in exacerbations was seen in exacerbations treated with corticosteroids of all intensities, and was consistent between the two trials.

- *Analysis of different subject populations defined by behavior during the trials*

Protocols 008 and 009 defined an analysis of an "acceptable" subject population; this consisted of subjects without major protocol violations and excluded discontinuers. For protocol 008 major protocol violations were:

1. Medical history likely to impact efficacy e.g. chronic bronchitis
2. Length of run-in <3 weeks
3. BDP dose not stable (within 50% of visit 3 dose) for at least 21 days during run-in
4. Mean daily total asthma symptom score <2.5 during the 14 days prior to visit 3
5. Dose of double-blind treatment received <0.014 mg/kg/IgE(IU/ml) per 4 weeks
6. Disallowed concomitant medication in doses and duration likely to impact efficacy, e.g. prednisolone
7. Change in BDP maintenance dose by >50% for >28 days outside of an asthma exacerbation
8. Patient non compliant
9. Beta-agonist within 4 hours of spirometry (only spirometric data)

For protocol 009 protocol violations also included:

1. Baseline IgE (measured at visit 1) level <20 IU/ml
2. Baseline (visit 3) BDP dose <3 puffs per day or >18 puffs per day
3. Percent of predicted FEV-1 >100% and patient not sufficiently symptomatic according to Diary
4. FEV_1 reversibility <10%

The criteria for noncompliance and for use of β-agonists within 4 hours of spirometry were omitted. Table 34 shows the results of the submitted analysis of the "acceptable" subject population.

Table 34. Subjects with exacerbations in "acceptable" population*

		Omalizumab	Placebo	Omalizumab	Placebo
Trial		Stable steroid phase		Steroid reduction phase	
008	*(ITT population)*	*(268)*	*(257)*	*(268)*	*(257)*
	"acceptable" population	248	226	239	210
	subjects with ≥1 exacerbation in " acceptable" population	11%	16%	15%	20%
	p-value	*0.092*		*0.094*	
009	*(ITT population)*	*(274)*	*(272)*	*(274)*	*(272)*
	"acceptable" population	242	215	236	204
	subjects with ≥1 exacerbation in " acceptable" population	10%	24%	11%	19%
	p-value	*0.001*		*0.021*	

*includes imputation

The effect size is smaller for the "acceptable" population. Genentech speculates that the loss of statistical significance in trial 008 was due to the exclusion of premature discontinuers**.** For this reason they performed an analysis of trial 008's primary endpoint excluding major protocol violators only (Table 35). From this Genentech concluded that for trial 008, "the acceptable patient population was impacted due to the larger number of dropouts in the placebo group."

Table 35. Trial 008: Subjects with exacerbations, excluding "major" protocol violators*

	Omalizumab	Placebo	Omalizumab	Placebo
	Stable steroid phase		Steroid reduction phase	
(ITT population)	*(268)*	*(257)*	*(268)*	*(257)*
subjects excluding major protocol violators	257	244	257	242
subjects with ≥1 exacerbation in nonexcluded population	14%	23%	21%	31%
p-value	0.009		0.005	

*includes imputation

The results of the exclusion of major protocol violators show that the major protocol violations did not affect the results. Upon request, Genentech performed an analysis with exclusion of premature discontinuers only, to discern the effect on the analysis of the premature discontinuers. The treatment difference narrowed, with a notable lessening of statistical significance compared to the primary analysis in trial 008 and in the steroid reduction phase of trial 009. These results support Genentech's conclusions quoted immediately above.

Table 36. Trials 008 and 009: Subjects with exacerbations (trial completers)

		Omalizumab	Placebo	Omalizumab	Placebo
Trial		Stable steroid phase		Steroid reduction phase	
008	*(ITT population)*	*(268)*	*(257)*	*(268)*	*(257)*
	completers	255	234	249	223
	subjects with ≥1 exacerbation among completers	11%	16%	15%	22%
	p-value	*0.08*		*0.054*	
009	*(ITT population)*	*(274)*	*(272)*	*(274)*	*(272)*
	completers	261	245	257	233
	subjects with ≥1 exacerbation among completers	11%	24%	10%	18%
	p-value	*<0.001*		*0.013*	

*includes imputation

Comments

The intent of the "acceptable" subject analysis was evidently to discern the effect of treatment based upon a "pure" population of subjects who completed the trial, obeying all major protocol rules. The interpretation of this analysis is difficult, as it excludes subjects for various reasons. However, the results were consistent with those of the primary endpoint analysis, showing somewhat less statistical certainty in the 008 trial.

The results of selective exclusion of major protocol violators only from the "acceptable" subject analysis are consistent with the analyses presented above using different imputation techniques. They show that the protocol-defined method of assigning exacerbations to dropouts skewed the determination of the level of statistical significance. This result is supported by the results of the CBER-requested analysis of subjects excluding premature discontinuers.

CBER sensitivity analyses of primary endpoint

- *Analysis of effect by site*

CBER examined the treatment effect by site, calculated as the proportion of subjects with ≥1 exacerbation, using observed counts (Table 37). In the table, a negative value signifies that the proportion of subjects in a treatment group with ≥1 exacerbation were lower in placebo; a positive value indicates a benefit of omalizumab.

Table 37. Numbers of sites in categories of intertreatment differences in proportions of subjects with exacerbations (placebo- omalizumab)

	Difference in proportions of subjects with ≥1 exacerbation (Placebo-Omlzmb)	Number of Sites (All sites*)		Number of Sites (Larger sites)		
		Trial 008	Trial 009*	Trial 008 # of sites (N>20)	Trial 009 # of sites (N>20)	Trial 009 # of sites (N>12)
Stable steroid phase	(-)	5	5	3	2	2
	0	5	10	1	0	0
	(+)	16	26	12	9	15
Steroid reduction phase	(-)	6	10	5	5	5
	0	3	11	1	0	0
	(+)	17	20	10	6	12

*table omits a site in trial 009 that enrolled a placebo subject only

Comment

A greater number of overall sites had a treatment effect (expressed in proportions of subjects with exacerbations) in the stable steroid phases of both trials and in the steroid stabilization phase of trial 008. However, the number of sites with a treatment effect in the steroid reduction phase of

trial 009 was about equal to the number with no effect (or an advantage of placebo). These proportions of sites held when the analysis was restricted to larger sites. However, if a slightly different cutoff value was chosen for trial 009, more sites reported a benefit of omalizumab in the steroid reduction period.

Overall, the site analysis points out a weakness in the results that probably derives from the small effect size, but is not a critical issue in deciding upon the adequacy of the data set.

- *Analysis of effect on protocol- and non-protocol-defined exacerbations*

Since not all exacerbations met protocol-defining criteria, CBER analyzed whether there was a selective effect only on the more significant, protocol-defined exacerbations. Analysis of the mean number of observed exacerbations defined informally by investigators and protocol-defined shows that the incidence of both types of exacerbations was lowered in the active arm compared to placebo (Table 38).

Table 38. Trial 008 CBER analysis: Comparison of protocol- and nonprotocol-defined observed asthma exacerbations for stable steroid and steroid reduction phases*

Trial	Phase		Protocol-defined		Nonprotocol	
			Omalizumab	Placebo	Omalizumab	Placebo
008	Stable steroid	*Subjects*	*268*	*257*	*268*	*257*
		exacerbations (mean/subject)	36 (0.13)	58 (0.23)	7 (0.03)	22 (0.09)
	Steroid reduction	*Subjects*	*258*	*238*	*258*	*238*
		Exacerbations (mean/subject)	44 (0.17)	60 (0.23)	24 (0.09)	39 (0.15)
009	Stable steroid	*Subjects*	*274*	*272*	*274*	*272*
		Exacerbations (mean/subject)	29 (0.11)	78 (0.29)	15 (0.05)	15 (0.06)
	Steroid reduction	*Subjects*	*261*	*245*	*261*	*245*
		Exacerbations (mean/subject)	32 (0.12)	54 (0.22)	32 (0.12)	51 (0.21)

*average exacerbation/subject in parentheses. The population total for steroid reduction excludes those who discontinued during stable phase, unlike The submitted analyses

- *Analysis of the effect on severity of asthma exacerbations*

CBER analyzed the severity of asthma exacerbation as defined by the investigators (Table 39). These results corroborate the conclusions drawn from the analysis of the intensity of corticosteroid treatment used for asthma exacerbations (see above, requested analysis). While omalizumab decreased the occurrence of exacerbations, the severity of the ones that occurred was not altered.

Table 39. Trials 008 and 009: Investigator-assigned severity of observed protocol-defined asthma exacerbations (number and percent of total exacerbations)

Trial	Phase	Omalizumab				Placebo			
		Mild	Moderate	Severe	TOTAL	Mild	Moderate	Severe	TOTAL
008	Stable steroid	5 *14%*	28 *78%*	3 *8%*	36 *100%*	5 *9%*	49 *84%*	4 *7%*	58 *100%*
	Steroid reduction	6 *14%*	37 *84%*	1 *2%*	44 *100%*	10 *17%*	45 *76%*	5 *8%*	59 *100%*
009	Stable steroid	7 *24%*	19 *66%*	3 *10%*	29 *100%*	13 *17%*	54 *69%*	11 *14%*	78 *100%*
	Steroid reduction	3 *10%*	25 *81%*	4 *13%*	31 *100%*	7 *13%*	41 *76%*	6 *11%*	54 *100%*

- *Analysis of the duration of effect to the end of the steroid reduction phase*

CBER examined the risk of protocol-defined exacerbations as a function of subject time in the trial (Table 40). In this analysis, all subjects who enter a time interval are counted for that interval. This analysis shows that there is no diminution in the effect of omalizumab over the duration of the core period for either trial.

Table 40. Trials 008 and 009: Risk of exacerbations by treatment group over core period

		Omalizumab		Placebo		Relative Risk (Omlzmb/ Placebo)
	Interval of trial (days)	Subjects at risk	exacerbations/ subject	Subjects at risk	exacerbations/ subject	
Trial 008	0-29	268	0.045	257	0.058	0.8
	30-59	266	0.034	252	0.071	0.5
	60-89	262	0.038	247	0.073	0.5
	90-119	262	0.034	240	0.079	0.4
	120-149	258	0.054	236	0.051	1.1
	150-179	253	0.047	230	0.096	0.5
	180-209	250	0.056	225	0.062	0.9
	210-239	19	0.000	20	0.000	0.0
Trial 009	0-29	274	0.036	272	0.088	0.4
	30-59	270	0.022	265	0.091	0.2
	60-89	268	0.022	262	0.061	0.4
	90-119	267	0.041	255	0.071	0.6
	120-149	264	0.045	247	0.065	0.7
	150-179	261	0.034	244	0.074	0.5
	180-209	258	0.027	237	0.059	0.5
	210-239	34	0.000	35	0.057	0.0

- *Analysis of effect by corrected nominal dose*

CBER correlated a measure of efficacy, the proportions of subjects with ≥1 exacerbation, with the administered monthly dose per kilogram (per IgE) of subject mass. Nominal dose was corrected for baseline subject body mass and IgE. In trial 008, corrected nominal monthly dose varied from 0.011 mg/kg/IU (IgE)/ml to 0.177 mg/kg/IU (IgE)/ml; in trial 009, corrected nominal dose varied from 0.006 mg/kg/IU (IgE)/ml to 0.105. Table 41 shows that there was no diminution of effect with the lower corrected nominal doses.

Table 41. Numbers and proportions of subjects with ³1 exacerbation, by corrected monthly dose*

			Stable steroid		Steroid reduction	
	monthly mg/[kg x IgE]		Omalizumab	Placebo	Omalizumab	Placebo
Trial 008	0.01 to <0.02	*n*	*27*	*29*	*27*	*29*
			3 (11)	3 (10)	7 (26)	4 (14)
	0.02 to <0.03	*n*	*119*	*125*	*119*	*125*
			13 (11)	21 (17)	15 (13)	28 (22)
	0.03 to <0.05	*n*	*78*	*63*	*78*	*63*
			6 (8)	13 (21)	11 (14)	12 (19)
	0.05 to <0.07	*n*	*16*	*25*	*16*	*25*
			4 (25)	4 (16)	1 (6)	4 (16)
	0.07 to <0.11	*n*	*25*	*12*	*25*	*12*
			3 (12)	4 (33)	5 (20)	1 (8)
	>=0.11	*n*	*3*	*3*	*3*	*3*
			1 (33)	2 (67)	0 (0)	2 (67)
	total n		*268*	*257*	*268*	*257*
Trial 009	0.01 to <0.02	*n*	*45*	*45*	45	45
			3 (7)	12 (27)	*3 (7)*	*6 (13)*
	0.02 to <0.03	*n*	*139*	*128*	139	128
			13 (9)	28 (22)	14 (10)	24 (19)
	0.03 to <0.05	*n*	*66*	*71*	*66*	*71*
			9 (14)	17 (24)	7 (11)	12 (27)
	0.05 to <0.07	*n*	*16*	*15*	*16*	*15*
			2 (13)	2 (13)	1 (6)	1 (7)
	0.07 to <0.11	*n*	*7*	*13*	*7*	*13*
			0 (0)	4 (31)	1 (14)	1 (8)
	>=0.11	*n*	*1*	*0*	*1*	*0*
			0 (0)	0	0 (0)	0
	total n		*274*	*272*	*274*	*272*

*nominal 4-week dose was corrected for baseline body mass and serum IgE

Submitted subset analyses of the primary endpoint

Table 42 and Table 43 show a categorization of the exacerbation data as presented by Genentech (*including imputation*) into numbers of subjects with 0 or ≥1 exacerbation. Since the great majority of subjects were "White," by far most of the data were contributed by this group, and there is little knowledge to be gained in the analysis of other groups. A similar conclusion can be made regarding the age groups: by far most of the data were contributed by the largest age group, those 18-64 years old. In both trials omalizumab exerted an effect in both sexes, but the effect was somewhat more pronounced in women. Efficacy was maintained in those with symptom scores >4 combined with FEV_1 ≤65%.

Table 42. Trial 008: Subjects with ³1 protocol-defined exacerbation, by subgroup, including imputation (% per group in parentheses)

Subgroup			Stable steroid phase		Steroid reduction phase	
			Omalizumab	Placebo	Omalizumab	Placebo
Ethnicity	White	*N/subgroup*	*238*	*229*	*238*	*229*
		n (%)	33 (14)	50 (22)	46 (19)	70 (31)
	Black	*N/subgroup*	*21*	*16*	*21*	*16*
		n (%)	5 (24)	8 (50)	12 (57)	9 (56)
	Oriental	*N/subgroup*	*1*	*3*	*1*	*3*
		n (%)	0	0	0	0
	Other	*N/subgroup*	*8*	*9*	*8*	*9*
		n (%)	0	1 (22)	2 (25)	4(44)
Combined asthma category	$FEV_1 \leq 65\%$ and total symptom score >4	*N/subgroup*	*58*	*53*	*58*	*53*
		n (%)	13 (22)	19 (36)	14 (24)	28 (53)
	Others	*N/subgroup*	*210*	*204*	*210*	*204*
		n (%)	25 (12)	41 (20)	43 (20)	55 (27)
Sex	Male	*N/subgroup*	*104*	*111*	*104*	*111*
		n (%)	17 (16)	23 (21)	21 (20)	37 (33)
	Female	*N/subgroup*	*164*	*146*	*164*	*146*
		n (%)	21 (13)	37 (25)	36 (22)	46 (31)
Age	12-17	*N/subgroup*	*20*	*21*	*20*	*21*
		n (%)	1 (5)	6 (29)	2 (10)	8 (38)
	18-64	*N/subgroup*	*241*	*229*	*241*	*229*
		n (%)	36 (15)	52 (23)	53 (22)	73 (32)
	65	*N/subgroup*	*7*	*7*	*7*	*7*
		n (%)	1 (14)	2 (29)	2 (29)	2 (29)

Table 43. Trial 009: Subjects with ³1 protocol-defined exacerbation, by subgroup, including imputations (% per group in parentheses)

Subgroup			Stable steroid phase		Steroid reduction phase	
			Omalizumab	Placebo	Omalizumab	Placebo
Ethnicity	White	*N/subgroup*	*256*	*242*	*256*	*242*
		n (%)	32 (12)	75 (31)	39 (15)	73 (30)
	Black	*N/subgroup*	*11*	*11*	*11*	*11*
		n (%)	2 (18)	3 (27)	3 (27)	4 (36)
	Oriental	*N/subgroup*	*2*	*6*	*2*	*6*
		n (%)	1 (50)	1 (17)	0	1 (17)
	Other	*N/subgroup*	*5*	*13*	*5*	*13*
		n (%)	0	4 (31)	1 (20)	3 (23)
Combined asthma category	$FEV_1 \leq 65\%$ and total symptom score >4	*N/subgroup*	*60*	*59*	*60*	*59*
		n (%)	12 (20)	23 (39)	9 (15)	17 (29)
	others	*N/subgroup*	*214*	*213*	*214*	*213*
		n (%)	23 (11)	60 (27)	34 (16)	64 (30)
Sex	Male	*N/subgroup*	*141*	*127*	*141*	*127*
		n (%)	19 (13)	32 (25)	20 (14)	28 (22)
	Female	*N/subgroup*	*133*	*145*	*133*	*145*
		n (%)	16 (12)	51 (35)	23 (17)	53 (37)
Age	12-17	*N/subgroup*	*18*	*17*	*18*	*17*
		n (%)	2 (11)	3 (18)	1 (6)	5 (29)
	18-64	*N/subgroup*	*237*	*246*	*237*	*246*
		n (%)	28 (12)	78 (32)	39 (16)	72 (29)
	65	*N/subgroup*	*19*	*9*	*19*	*9*
		n (%)	5 (26)	2 (22)	3 (16)	4 (44)

Submitted subgroup analyses in pooled data sets

Table 44 shows a pooled analysis of data from trials 008 and 009. The analyses shown below are based on the same analytical technique that was used in the primary analysis of the individual trials. All comparisons were statistically significant, except as noted with an asterisk. A consistent finding was a lack of statistical significance for the subjects with the least impairment of airflow (FEV_1), with the mean exacerbation rates being equal during the steroid stabilization phase. A more detailed analysis of the effect on exacerbations correlated with FEV_1 is presented in the Appendix (Table 151). These data suggest that the treatment effect in the critical efficacy trials was restricted to subjects with the lower FEV_1 at baseline.

Table 44. Mean exacerbations/subject in submitted pooled (trial 008 and 009) analysis of subgroups

Subgroup		*All subjects*	Stable steroid phase		Steroid reduction phase	
			Omalizumab	Placebo	Omalizumab	Placebo
Ethnicity	White	*965*	0.26	0.58	0.33	0.69
	Black	*59*	0.75*	1	1.13*	1.15
	Other	*47*	0.06	0.61	0.44*	0.65
Combined asthma category	$FEV_1 \leq 65\%$ and total symptom score >4	*230*	0.42	0.78	0.42	0.83
	Others	*841*	0.24	0.55	0.36	0.67
FEV_1	>80%	*234*	0.26*	0.37*	0.41*	0.41*
	>60% to ≤80%	*546*	0.21	0.58	0.29	0.66
	≤60%	*291*	0.42	0.82	0.51	1.03
Sex	Male	*483*	0.33	0.5	0.38	0.65
	Female	*588*	0.24	0.68	0.37	0.76
Age	12-17	*76*	0.08	0.66	0.21	0.74
	18-64	*953*	0.03	0.6	0.4	0.71
	≤65	*42*	0.23*	0.63	0.23*	0.69

*not statistically significant in comparison to placebo; all other comparisons, p<0.05 at least

Submitted analyses of groups dichotomized by allergen sensitivities (dichotomized at 2), history of atopic dermatitis (yes or no), and baseline BDP dose (dichotomized at 8 puffs/day) showed a consistent treatment effect.

Genentech submitted analyses of mean exacerbation rates by dosing schedule in the pooled population from trials 008 and 009 (Table 45).

Table 45. Mean exacerbations/subject in submitted pooled (trial 008 and 009) analysis by dosing frequency

Dosing Frequency		Stable steroid phase		Steroid reduction phase	
	All subjects	Omalizumab	Placebo	Omalizumab	Placebo
Every 2 weeks	*456*	0.38	0.75	0.4	0.82
Every 4 weeks	*615*	0.2	0.49	0.36	0.62

Note: All intertreatment comparisons, p≤0.01 at least

The submitted analysis of median percent reduction in corticosteroid dosing was consistent with the analysis of the primary endpoint.

Comments

The submitted pooled analysis was consistent with the individual analyses. The most notable finding was in the analysis by FEV_1, where there was little effect in subjects with FEV_1 >80%, and in the gender analysis, where there appeared a larger effect in females than in males.

CBER's subset analyses of primary endpoint

1. Using submitted subset categories

CBER performed subset analyses on the observed exacerbation data set using submitted subset categories (See Appendix Table 140 and Table 141). The analysis of observed exacerbations was consistent with the analysis using imputed counts as displayed by Genentech.

2. Severity and other subgroup analyses

Using the observed exacerbation data base, CBER performed an analysis of efficacy for both trials by surrogates of severity (doctor's visits, quartiles of baseline BDP usage), IgE, numbers of allergens to which subjects were sensitive, weight, and age (see Appendix Table 142 through Table 150). These analyses do not show a loss of effect at extremes of age, weight, numbers of allergen sensitivities, or surrogates of disease severity within the enrolled population.

Conclusions about primary endpoint

Exacerbations were decreased in omalizumab -treated subjects in both trials, over both stable steroid and steroid reduction phases. The primary method of imputation enlarged the treatment effect, but other imputation methods were consistent with this primary method. Treatment schedule was not a critical factor in determining efficacy, nor were measures of extent of allergy or disease severity within this relatively non-severe group of asthmatic subjects.

The effects were driven by a small number of subjects, since the majority of subjects did not have any exacerbations.

Further subgroup analyses, combining the results of trials 008 and 009 with those of trial 010 (also reviewed in this document), will be shown later in this document.

Analysis of potential unblinding of subjects or investigators

CBER examined injection site reactions as an indication of potential biasing of subjects or investigators. Table 46 shows that a slightly greater proportion of subjects in trial 008, but not 009, reported any injection site reaction. In both trials, slightly greater proportions of subjects reported any symptom between a visit (a longer reaction), but the proportions of moderate-severe burning, itching, and hives were similar.

Table 46. Trials 008 and 009: Subjects (n,% of group) with injection site reactions

	Trial 008		Trial 009	
	Omalizumab *n=268*	Placebo *n=257*	Omalizumab *n=274*	Placebo *n=272*
Any symptom	267 (99)	255 (99)	271 (98)	271 (99)
Between visit symptom	101 (38)	92 (36)	133 (49)	115 (42)
Moderate-severe burning itching hives	 15 (6) 9 (3) 6 (2)	 15 (6) 6 (2) 2 (1)	 12 (4) 14 (5) 3 (1)	 12 (4) 13 (5) 6 (2)

Comments

Injection site reactions, which could signify to subjects what treatment they were receiving, were balanced in frequency and severity and thus were not likely to affect the outcome of the trial substantially.

Secondary endpoints

- *Numbers of subjects experiencing at least one exacerbation*

The numbers of subjects with at least one exacerbation (including imputation) can be gleaned from the previous tables showing exacerbation counts. Genentech applied the Cochran-Mantel-

Haenszel test stratified by treatment schedule in the statistical analysis. For the steroid stabilization phase, the p-value of the difference between omalizumab and placebo was 0.009 in trial 008 and <0.001 in trial 009. For the steroid reduction period, p-values for the differences between the treatment arms in trials 008 and 009 were 0.004 and <0.001, respectively.

Comments

This secondary endpoint does not add to the understanding of exacerbation rates gained in the analysis of the primary endpoint.

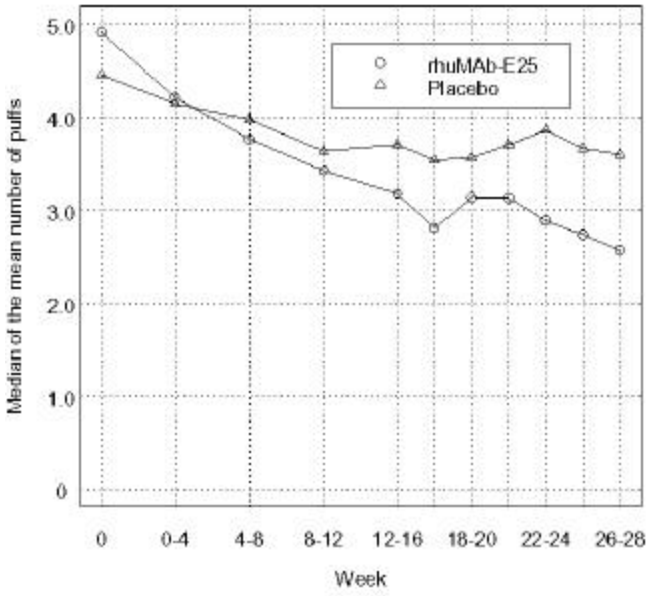
Genentech notes for the steroid reduction period of 008 that the every-2-week schedule was statistically different from the every-4-week schedule using the Breslow-Day test (p=0.026). In this phase of trial 008, efficacy was seen in the Q2w group, but little efficacy was seen in the Q4w group. This pattern of differential efficacy is not found in the stable steroid phase of trial 008, nor is it evident in either period of trial 009.

- *Number of puffs of rescue medication*

Genentech calculated the mean number of puffs of albuterol taken daily during 4-week intervals between visits during the stable steroid phase and during 2-week periods during the steroid reduction phase of trials 008 and 009. Figure 5 and Figure 6 show the median values of the mean number of puffs of albuterol taken over these time intervals. Intertreatment comparisons were statistically significant at ≤0.002 at weeks 8, 12, and 16 in trial 008, and were statistically significant at ≤0.001 at weeks 4, 8, 12, and 16 in trial 009; they were not tested in the steroid reduction phases.

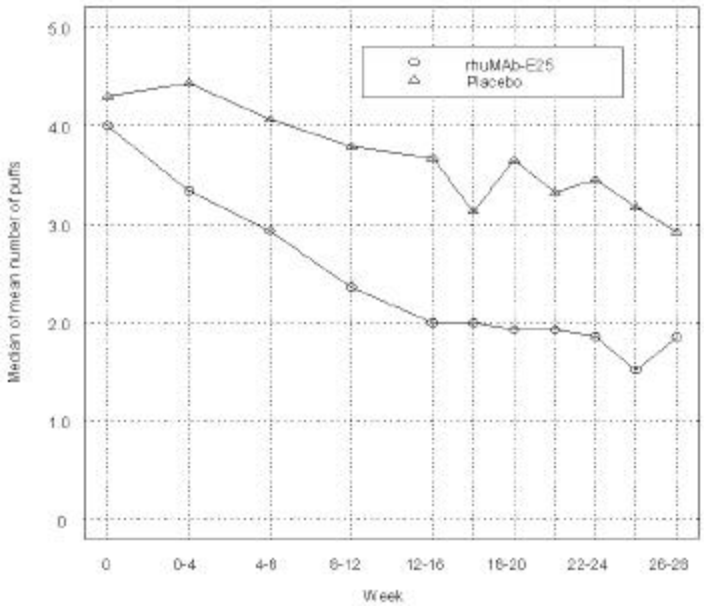
In both trials there was an approximate 1-puff advantage of omalizumab over placebo in the median of the mean number of daily puffs of albuterol at the end of the core period. The clinical significance of this should be interpreted in light of the fact that a typical dose administered for an episode of bothersome wheezing (not necessarily an exacerbation) is 2 puffs.

Figure 5. Trial 008: Medians of the mean puffs of albuterol taken daily



Subject numbers: Omalizumab:265, dropping to 244, Placebo: 255, dropping to 222

Figure 6. Trial 009: Medians of the mean puffs of albuterol taken daily (intent-to-treat population)



Subject numbers: Omalizumab:270, dropping to 251, Placebo: 266, dropping to 229

Comments

Use of albuterol decreased in all subjects on average, but more so in the omalizumab-treated group. The greater lowering of the use of immediate-acting b2-agonist MDI medication supports the finding of a reduction in exacerbations. However, a 1-1.5-puff daily difference in the use of albuterol is not clinically significant, as the use of the medication is usually 2 puffs at a time.

- *Reduction in the dose of BDP*

Based in part upon discussions with FDA, in lieu of performing the protocol-defined endpoint analyses concerning corticosteroid reduction, Genentech analyzed the data more generally as the proportion of subjects with complete withdrawal of the dose of BDP and with graded percents

reduction in the dose of BDP (Table 47). Subjects who dropped out before the steroid reduction phase were imputed as having no reduction in their BDP dose. For patients who prematurely discontinued in the reduction phase their last recorded dose of BDP was used as their final dose. There was no noticeable difference in effect when considering treatment schedules. The submitted Cochran-Mantel-Haenszel test on the ranks (using the "75%-100%" rank, but not the "100%" rank) yielded a p-value <0.001 for both trials.

Table 47. Trials 008 and 009: Subjects (proportion of group) with reductions in inhaled corticosteroid dosing (intent-to-treat analysis)

Percent reduction in BDP	Trial 008		Trial 009	
	Omalizumab *n=268*	Placebo *n=257*	Omalizumab *n=274*	Placebo *n=272*
100%	*106 (40%)*	*49 (19%)*	*118 (44%)*	*53 (19%)*
75% to ≤100%	141 (53%)	89 (35%)	165 (60%)	92 (34%)
50% to < 75%	53 (20%)	52 (20=%)	51 (19%)	57 (21%)
25% to < 50%	25 (9%)	34 (13%)	20 (7%)	33 (12%)
0% to < 25%	44 (16%)	66 (26%)	30 (11%)	77 (28%)
< 0%	5 (2%)	16 (6%)	8 (3%)	13 (5%)

In trial 008, the median percent reduction in corticosteroid was 75% in omalizumab-treated subjects and 50% in placebo-treated subjects; in trial 009, the median percent reduction was 83% in omalizumab-treated subjects and 50% in placebo-treated subjects.

Comment

The imputation technique used by Genentech was reasonable, and in this case would have biased against the product. In both trials omalizumab treatment was associated with a greater proportion of subjects lowering or withdrawing from corticosteroids.

CBER's sensitivity analysis of reductions in corticosteroid use

CBER calculated the numbers of subjects with complete withdrawal of corticosteroid dosing during the steroid reduction phase, as a function of the daily dose they were on at the visit 3 baseline (Table 48). The dosing groups in Table 48 represented the most common dosing groups, and they omit a very small number of subjects in either trial. The proportions of subjects with complete discontinuation decreased for both groups with increasing daily dose of BDP, but there was a higher proportion of complete discontinuations in omalizumab in all groups.

Table 48. Trials 008 and 009: Numbers (proportion of group) with 100% reduction in BDP dosing, by baseline dose of BDP

	Trial 008			Trial 009	
Baseline BDP dose (μg/day)*	Omalizumab	Placebo	Baseline BDP dose (μg/day)	Omalizumab	Placebo
420	45/77 (58)	18/80 (23)	500	30/59 (51)	11/55 (20)
504	31/89 (35)	17/74 (23)	600	34/73 (47)	16/67 (24)
672	16/57 (28)	12/58 (21)	800	26/50 (52)	11/47 (23)
840	10/39 (26)	2/37 (5)	1000	20/60 (33)	8/57 (14)
-	-	-	1200	6/27 (22)	4/28 (14)
*Total subjects***	*262*	*249*	*Total subjects*	*269*	*254*

* Most common dosing groups
*Totals less than total enrolled, since table shows only dosing groups with adequate subjects for comparisons

Comments

The trials were consistent with each other in showing that there was more reduction in corticosteroid treatment in omalizumab-treated subjects than in placebo subjects, regardless of original dose of inhaled corticosteroid. About 20-25% more omalizumab-treated subjects were able to completely eliminate inhaled corticosteroid use. Most, but not all of these subjects in these trials were in the lower-to-medium corticosteroid use categories (Appendix Table 138).

- *Global evaluation of treatment effectiveness*

The global evaluation of treatment effectiveness was used by both the subject and investigator at the end of the steroid reduction phase. Table 49 shows the subjects' and investigators' global evaluations of treatment effectiveness. Genentech reports that the Cochran-Mantel-Haenszel test showed statistical significance for comparisons of subject and investigator evaluations for both trials ($p<0.001$ for both sets of comparisons).

Table 49. Trials 008 and 009: Global evaluations of treatment effectiveness, end of steroid reduction phase (% of group)

Trial	Rating	Subjects' evaluation*			Investigators' evaluation*		
		Omlzmb	Placebo	Difference	Omlzmb	Placebo	Difference
		n=256	*n=244*		*n=256*	*n=243*	
008	Excellent	17.6	7.4	10.2	14.8	4.5	10.3
	Good	43	30.7	12.3	38.3	28.8	9.5
	Moderate	21.9	27	-5.1	28.9	26.3	2.6
	Poor	12.9	27.5	-14.6	12.9	34.6	-21.7
	Worsening	4.7	7.4	-2.7	5.1	5.8	-0.7
009		*n=262*	*n=258*		*n=263*	*n=259*	
	Excellent	26	8.1	17.9	17.5	5.8	11.7
	Good	43.5	34.5	9	48.7	29	19.7
	Moderate	19.8	30.6	-10.8	22.1	33.2	-11.1
	Poor	8.4	21.7	-13.3	10.6	27.4	-16.8
	Worsening	2.3	5	-2.7	1.1	4.6	-3.5

1. Excellent (complete control of asthma)
2. Good (marked improvement of asthma)
3. Moderate (discernible, but limited improvement in asthma)
4. Poor (no appreciable change in asthma)
5. Worsening of asthma

Comments

The global evaluation appears to be biased toward showing improvement, consisting of 3 positive categories (excellent, good, moderate improvement), 1 of no change, and 1 of worsening. For both trials and for both subjects and investigators, the subjects on omalizumab responded more positively.

Tertiary endpoints

- *"Asthma-free" days*

The protocol's term is a misnomer in that the definition of "asthma-free" allows for some daytime symptoms and the daily use of 2 puffs of albuterol rescue medication. (Note also that while the protocol specified that the PEFR should be ≥80% of best, Genentech analyzed the data using a more stringent PEFR criterion of ≥90%). However, it can be used as an indicator of efficacy. Table 50 shows the proportions of low symptom days during the stable steroid phase for trials 008 and 009. The median proportion of low symptom days in omalizumab and placebo subjects in trial 008 was 0.03 and 0.01, respectively; in trial 009, 0.06 vs. 0 (p-value of 0.040 for trial 008 and <0.001 for trial 009).

The results are consistent with those of exacerbation and steroid reduction.

Table 50. Proportions of low-symptom days in trials 008 and 009

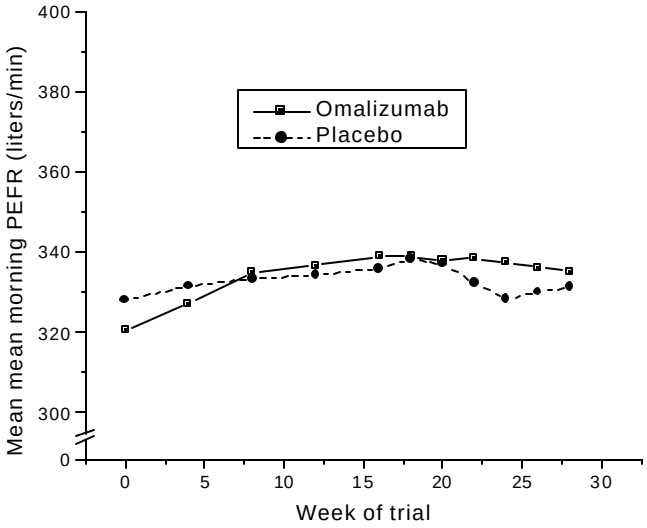
	Trial 008		Trial 009	
Proportion of low-symptom days	Omalizumab *n=266*	Placebo *n=255*	Omalizumab *n=271*	Placebo *n=268*
80% to <=100%	16 (6.0%)	3 (1.2%)	19 (7.0%)	10 (3.7%)
60% to < 80%	25 (9.4%)	12 (4.7%)	28 (10.3%)	13 (4.9%)
40% to < 60%	17 (6.4%)	16 (6.3%)	28 (10.3%)	19 (7.1%)
20% to < 40%	34 (12.8%)	31 (12.2%)	31 (11.4%)	25 (9.3%)
0% to < 20%	174 (65.4%)	193 (75.7%)	165 (60.9%)	201 (75.0%)

- *Mean morning PEFR, measured by visit*

As can be seen in Figure 7, in trial 008 there was a baseline imbalance and changes from baseline were small. For trial 009 (Figure 8), baseline morning PEFR were equivalent and maintained a

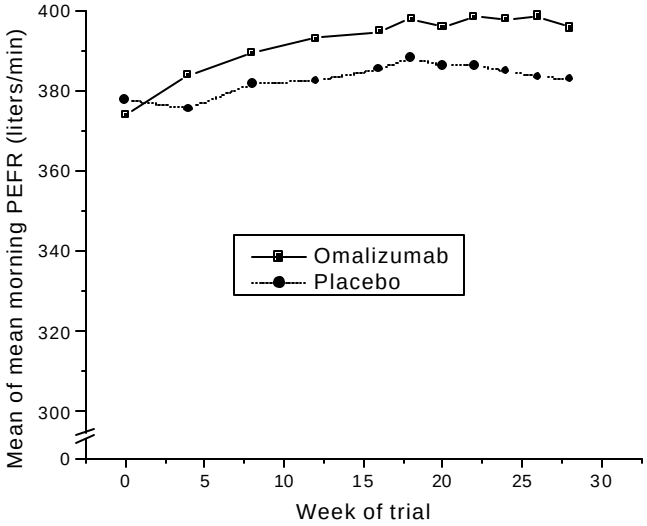
clinically insignificant, but consistent difference favoring omalizumab. Overall, the morning PEFR data are consistent with a clinically insignificant improvement with omalizumab.

Figure 7. Trial 008: Morning PEFR



Subject numbers: Omalizumab: 268 dropping to 245; Placebo, 257 dropping to 222

Figure 8. Trial 009: Morning PEFR



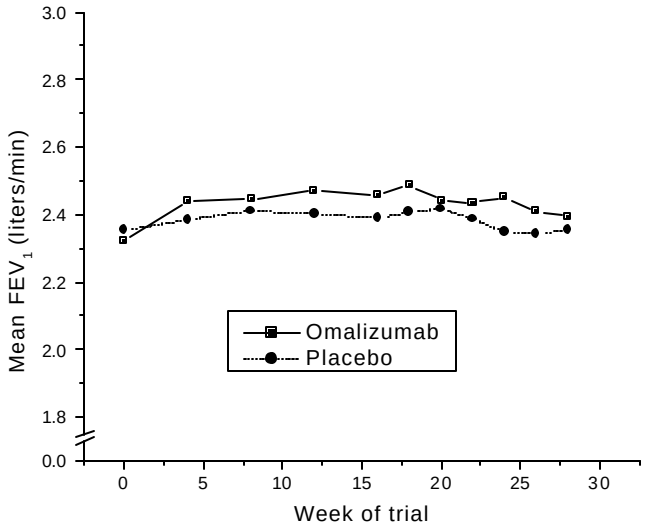
Subject numbers: Omalizumab: 273 dropping to 251; Placebo, 269 dropping to 230

- *Evening PEFR, measured by visit*
  The results for trials 008 and 009 were consistent with those for morning PEFR.
- *Difference between morning and evening PEFR, measured by visit*
  Differences between omalizumab- and placebo-treated groups were very slight and statistically insignificant where measured (stable steroid phase).

- *Mean FEV_1 , measured by visit*

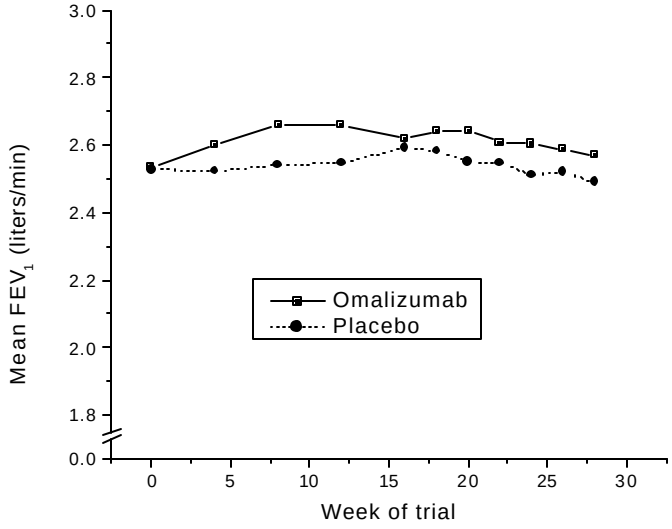
Figure 9 and Figure 10 show mean FEV_1 over the course of the core periods for trials 008 and 009. The changes from baseline are slight in both groups in both trials, and the intertreatment difference is slight.

Figure 9. Trial 008: Mean FEV_1



Subject numbers: Omalizumab: 268 dropping to 249; Placebo: 257 dropping to 223

Figure 10. Trial 009: Mean FEV_1



Subject numbers: Omalizumab: 274 dropping to 256; Placebo: 272 dropping to 233

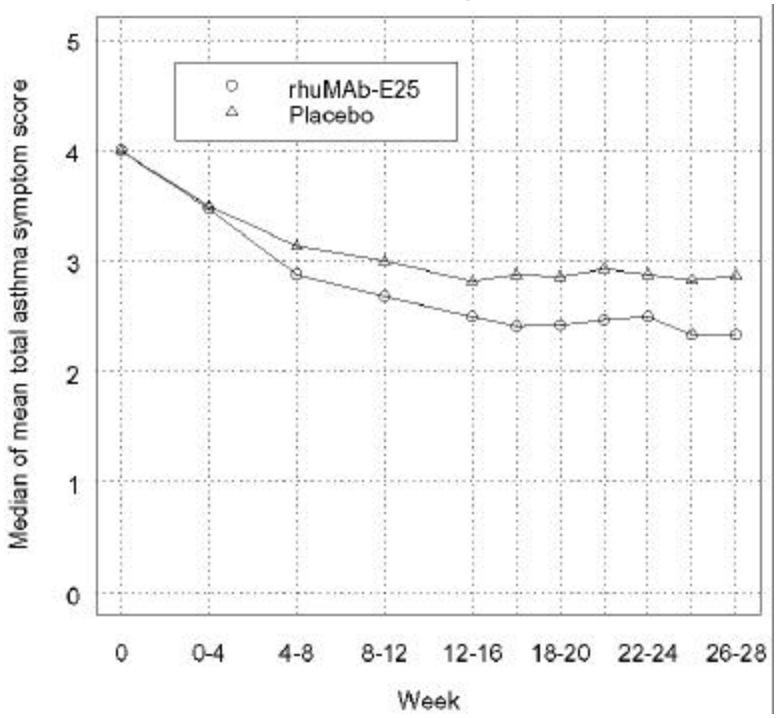
- *Mean FVC and FEF_{25-75}, measured by visit*

Results were consistent with those of FEV_1.

- *Mean total asthma symptom score, measured by visit*

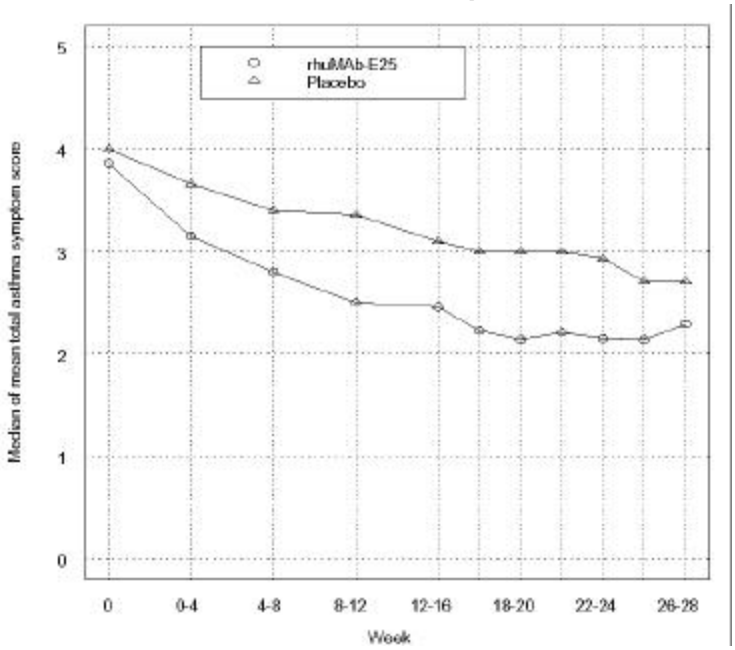
During the core period of trial 008, a difference appeared in the median of the mean score favoring active treatment, which increased and stabilized to about 0.5 points during the steroid reduction phase (Figure 11). In trial 009 a difference also appeared favoring active treatment: at the end of the stable steroid phase, the difference in the median score was about 0.6, and at the end of the steroid reduction phase, about 0.4 (Figure 12).

Figure 11. Trial 008: Median of mean total (nocturnal, morning, daily) asthma symptom score, 0-9 scale)



Subject numbers: Omalizumab: 265 dropping to 243; Placebo, 255 dropping to 222

Figure 12. Trial 009: Median of mean total (nocturnal, morning, daily) asthma symptom score, 0-9 scale)



Subject numbers: Omalizumab: 269 dropping to 248; Placebo, 266 dropping to 228

- *Nocturnal asthma symptom score, presence of morning asthma symptoms, and daytime asthma symptom score, measured by visit*

The results for these endpoints were consistent with those of the total asthma symptom score (see Appendix Table 152).

Comments

FEV_1 and PEFR measures are important in the evaluation of an asthma controller medication, representing the obstruction to outflow of air. These measures showed small, clinically insignificant differences that favored active treatment.

While the clinical meaning of the intertreatment difference in total asthma symptom score is not described, it should be kept in mind that the scale is from 0-9, suggesting that the difference is slight at best. Other subscale scores showed consistent differences.

Overall, these tertiary endpoints show small differences that suggest that the daily benefit is small.

Other variables

- *Quality of life questionnaire*

The quality of life instrument used in trials 008 and 009 was the Juniper asthma quality of life questionnaire. It consists of 32 questions grouped into symptom, activities, emotions, and environmental "domains" (the last are questions related to which stimuli in the environment stimulate asthmatic symptoms), each of which is scored from 1-7, where 1 corresponds to maximal severity or time with a symptom and 7 is no severity or time with a symptom. An overall score is assigned, which is the mean of the domain scores.

As a component of the activities domain, subjects were to pick 5 activities to be rated on the questionnaire throughout the trial. Genentech states that for these trials some subjects (numbers not detailed in the submission) did not follow the intended plan for rating the same activities. The primary analysis of the AQLQ data was on the questionnaire without these questions, for all

subjects. It was decided after the trial started that all subjects, regardless of age, were to fill out the adult version of the AQLQ. Results from 8 subjects in trial 008 and 25 in trial 009 who filled out a pediatric version of the questionnaire were not analyzed. Table 51 shows the overall results.

Table 51. Trials 008 and 009: Juniper AQLQ overall results (subjects with categorized changes in score)

	Trial 008				Trial 009			
	Stable steroid		Steroid reduction		Stable steroid		Steroid reduction	
	Omlzmb n=251	Placebo n=242	Omlzmb n=244	Placebo n=219	Omlzmb n=200	Placebo n=192	Omlzmb n=190	Placebo n=176
>= 1.5	28%	20%	32%	19%	21%	13%	26%	15%
1.0 to <1.5	16%	10%	17%	13%	15%	17%	19%	17%
0.5 to <1.0	18%	19%	17%	22%	23%	22%	20%	23%
0.0 to <0.5	20%	22%	16%	20%	25%	21%	23%	23%
<0	18%	28%	18%	27%	17%	27%	13%	22%

Table 52 shows the results for the overall score and the individual domain scores, in more condensed form.

Table 52. Subjects with any degree of worsening or an improvement from baseline of ³ 0.5 points in the Juniper asthma quality of life questionnaire

Domain	Trial 008				Trial 009			
	Stable steroid		Steroid reduction		Stable steroid		Steroid reduction	
	Omlzmb *N=251*	Placebo *N=240-242*	Omlzmb *N=243-244*	Placebo *N=218-219*	Omlzmb *N=198-200*	Placebo *N=191-192*	Omlzmb *N=189-190*	Placebo *N=175-176*
Overall (<0)	18%	28%	18%	27%	17%	27%	13%	22%
≥0.5	63%	50%	66%	53%	59%	52%	65%	55%
Activities (<0)	16%	27%	16%	26%	22%	30%	14%	28%
≥0.5 better	62%	50%	63%	52%	54%	52%	62%	52%
Emotions Worsening (<0)	20%	27%	21%	27%	14%	24%	13%	23%
≥0.5 better	63%	48%	62%	50%	57%	43%	63%	50%
Symptoms Worsening (<0)	17%	26%	19%	27%	18%	23%	14%	21%
≥0.5 better	65%	55%	67%	57%	65%	56%	67%	55%
Exposure Worsening (<0)	20%	28%	21%	24%	24%	23%	18%	21%
≥0.5 better	60%	48%	64%	55%	57%	58%	62%	54%

Comment

This quality of life questionnaire is more appropriately call an asthma-specific assessment tool. The tool actually evaluated here is a modified version of the standard questionnaire. Genentech has provided an assessment of the modified tool and the AQLQ with the varied subject-specified activities questions added (another version of the AQLQ that is modified from the intended use), and information on the correlation with other results in the trials. However, these assessments leave uncertain what the actual results would have been if the AQLQ had been performed properly. These results should be seen as suggestive only.

- *Missed school or work days; unscheduled medical contacts*

Table 53 shows the submitted analysis of the numbers missed school or work days due to asthma. The comparability of the subpopulations from which these data originate is not discussed. Numbers of subjects studied in the school days analysis was small, and conclusions on these data would be speculative. Numbers of work days missed due to asthma were less in the active-treatment

group in trial 008 but more in trial 009, suggesting that there is no appreciable effect in this parameter.

Table 53. Trials 008 and 009: Days of school or work missed due to asthma

Trial		Omalizumab	Placebo
008	School	*n=49*	*n=55*
	mean ± sd	0.49 ± 2.1	0.59 ±1.9
	Work	*n=242*	*n=232*
	mean ± sd	0.38 ± 1.4	0.72 ± 3.2
009	School	*n=51*	*n=38*
	mean ± sd	0.12 ± 0.48	1.25 ±3.88
	Work	*n=229*	*n=225*
	mean ± sd	0.51 ±1.7	0.44 ±1.5

Table 54 shows that the numbers of unscheduled medical contacts were low over the 28 weeks of the core period for each trial, and comparable between the two groups. The mean number of urgent care center or emergency room visits for either group was 0 for both trials.

Table 54. Trials 008 and 009: Mean unscheduled medical contacts (intent-to-treat population)

Trial	Omalizumab	Placebo
008	*n=268*	*n=257*
	0.26 ± 0.65	0.27 ± 0.62
009	*n=274*	*n=272*
	0.3 ± 0.88	0.31 ± 0.85

Comments

Unscheduled medical contact information suggests the non-severe condition of the asthma in the subjects enrolled in these trials. There was no appreciable effect of omalizumab on the parameters measured.

Extension phase efficacy evaluations in trials 008 and 009

Unblinding of core results

Genentech states that "a select list of individuals from Novartis and Genentech" knew the results from the core period, and that a confidentiality agreement was signed by each person. Genentech states, "Subjects, investigators, and the clinical team conducting the study remained blinded during the extension period of trial 008." However, members of the clinical team became aware of core results during the extension period of trial 009 for preparation of the BLA. Other clinical personnel were assigned to perform "clinical site maintenance activities" during the conduct of the extension period of trial 009.

Comments

Unblinding of results from the core period could potentially have affected the conduct of the extension period. These results were not considered primary and the definitive efficacy assessment is not derived from the extension period. However, this period's results are useful for their contribution of the knowledge of the duration of effects seen in the core period.

Summary of demographics and baseline characteristics/dropouts

As Table 19 and Table 20 show, not all subjects who completed the core period entered the extension phases of these trials, and dropouts during the extension phase continued to be higher in the active treatment group. In trial 008, about 91% of omalizumab subjects and 84% of placebo

subjects entered the extension phase; in trial 009, about 93% of omalizumab subjects and 84% of placebo subjects entered the extension phase. For both trials, demographic and baseline characteristics continued to be well matched (data not shown in this review).

Efficacy evaluations

- *Asthma exacerbations*

Asthma exacerbations meeting protocol requirements were defined somewhat differently from those in the core period: Like those in the core period, an aspect of the definition was the institution of oral or IV corticosteroids; however, doubling of inhaled corticosteroid was defined in relation to the immediately preceding dose, not baseline dose.

Trial 008

The protocols did not specify an analytical technique for the extension phase. Genentech presents observed data only with no inferential statistics (Table 55). Note that Table 55 is derived from information corrected by Genentech upon request (for trial 008 the original BLA analysis used exacerbations that had occurred in the followup period in addition to exacerbations that occurred in the extension period).

Table 55. Trial 008: Subjects with observed asthma exacerbations during the extension phase (extension phase definition of exacerbation)*

	Q2w		Q4w		Overall	
Number of exacerbations	Omlzmb *n=96*	Placebo *n=84*	Omlzmb *n=149*	Placebo *n=131*	Omlzmb *n=245*	Placebo *n=215*
0	73 *76%*	54 *64%*	121 *81%*	92 *70%*	194 *79%*	146 *68%*
1	18 *19%*	26 *31%*	23 *15%*	27 *21%*	41 *17%*	53 *25%*
>1	5 *5%*	4 *5%*	5 *3%*	12 *9%*	10 *4%*	16 *8%*
total ≥1	23 *24%*	30 *36%*	28 *19%*	39 *30%*	51 *21%*	69 *32%*

*Extension phase population

Trial 009

Table 56 shows exacerbation counts as presented by Genentech, using the extension phase population. Genentech presented no inferential statistics.

Table 56. Trial 009: Subjects with observed asthma exacerbations during the extension phase (extension phase definition of exacerbation)*

	Q2w		Q4w		Overall	
Number of exacerbations	Omlzmb *n=115*	Placebo *n=101*	Omlzmb *n=139*	Placebo *n=128*	Omlzmb *n=254*	Placebo *n=229*
0	88 *77%*	69 *68%*	114 *82%*	87 *68%*	202 *80%*	156 *68%*
1	23 *20%*	27 *27%*	21 *15%*	29 *23%*	44 *17%*	56 *25%*
>1	4 *3%*	5 *5%*	4 *3%*	12 *9%*	8 *3%*	17 *7%*
total ≥1	27 *24%*	32 *32%*	25 *18%*	41 *32%*	52 *21%*	73 *32%*

*Extension phase population

Sensitivity analysis of extension phase exacerbations: Core period definition of exacerbation

Upon request, Genentech provided analyses of extension phase exacerbations using the core period definition of an exacerbation. Table 57and Table 58 show the submitted analysis, which includes the entire trial population (not only extension phase subjects as in Table 55 and Table 56), showing observed exacerbations only.

Table 57. Trial 008: Subjects with observed asthma exacerbations during the extension phase (core period definition)*

	Q2w		Q4w		Overall	
Number of exacerbations	Omlzmb *n=106*	Placebo *n=101*	Omlzmb *n=162*	Placebo *n=156*	Omlzmb *n=268*	Placebo *n=257*
0	94 *89%*	85 *84%*	144 *89%*	128 *82%*	238 *89%*	213 *83%*
1	10 *9%*	13 *13%*	15 *9%*	17 *11%*	25 *9%*	30 *12%*
>1	2 *2%*	3 *3%*	3 *2%*	11 *7%*	5 *2%*	14 *6%*
total ≥1	12 *11%*	16 *16%*	18 *11%*	28 *18%*	30 *11%*	44 *17%*

*Entire trial population
p=0.04 (CMH stratified by dosing schedule)

Table 58. Trial 009: Subjects with observed asthma exacerbations during the extension phase (core period definition)*

	Q2w		Q4w		Overall	
Number of exacerbations	Omlzmb *n=127*	Placebo *n=122*	Omlzmb *n=147*	Placebo *n=150*	Omlzmb *n=274*	Placebo *n=272*
0	111 *87%*	100 *82%*	136 *93%*	118 *79%*	247 *90%*	218 *80%*
1	13 *10%*	18 *15%*	9 *6%*	21 *14%*	22 *8%*	39 *14%*
>1	3 *2%*	4 *3%*	2 *1%*	11 *7%*	5 *2%*	15 *6%*
total ≥1	16 *13%*	22 *18%*	11 *8%*	32 *21%*	27 *10%*	54 *20%*

*Entire trial population
p<0.01 (CMH stratified by dosing schedule)

Analyses of core protocol-defined exacerbation rates using the core protocol-defined method of imputation and imputation of the maximal number or single imputation (not shown) were consistent with the overall impression of the treatment effect gleaned from the observed exacerbation rates.

Upon request, Genentech provided an analysis of the maximal intensity of corticosteroids used in the treatment of core-period-defined extension phase exacerbations (Table 59). This analysis shows that as in the core period, the great majority of core-period-defined exacerbations were treated with oral corticosteroids. The qualification of corticosteroid use based on a doubling of inhaled corticosteroid, the least significant corticosteroid intervention, occurred more often in the placebo arm.

Table 59. Trials 008 and 009 extension period: Maximal corticosteroid used to treat exacerbations (core protocol definition)

	Trial 008		Study 009	
	Omalizumab (n=268)	Placebo (n=257)	Omalizumab (n=274)	Placebo (n=272)
Total number of exacerbations	36	64	32	70
Maximum steroid intensity				
IV steroid use	0 (0%)	2 (3%)	0 (0%)	3 (4%)
IM steroid use	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Oral steroid use	35 (97%)	59 (92%)	27 (84%)	55 (79%)
Doubling baseline BDP	0 (0%)	3 (5%)	3 (9%)	12 (17%)

Comments

Using the core period definition, the numbers of observed exacerbations decreased, which was expected. The corticosteroid treatment of extension period exacerbations was similar in intensity to that seen in the core periods.

The treatment effect of omalizumab on observed exacerbations was similar during the extension period to that in the stable steroid and steroid reduction phases. The effect did not disappear over the time of observation (52 weeks).

- *BDP usage*

Table 60 shows BDP usage at baseline (visit 3), at the end of the steroid reduction period, and for the 4 weeks prior to visit 19 (end of the extension period) for trials 008 and 009. In both trials, BDP usage dropped in both treatment groups during the core period (negative values of change), more so in the active group. During the extension phases the average usage of BDP in both groups increased slightly, by approximately the same amount.

Table 60. Trials 008 and 009: Use of BDP (mcg) at the end of extension phase compared to use during core period in extension phase subjects (means ± s.e.)

Phase of trial	Trial 008		Trial 009	
	Omalizumab	Placebo	Omalizumab	Placebo
Baseline of core*	*n=244*	*n=215*	*n=254*	*n=229*
	564 ± 9.4	552 ± 9.2	766 ± 15	777 ± 17
Change, baseline to end of steroid reduction	*n=244*	*n=215*	*n=254*	*n=229*
	-371± 15	-278 ± 17	-553 ± 20	-399 ± 24
Change, baseline to end of extension	*n=243*	*n=214*	*n=252*	*n=228*
	-322 ± 17	-227 ± 19	-485 ± 21	-322 ± 26

* Baseline values for all randomized subjects from the core period were not noticeably different from those of this selected population:

Baseline values for BDP use (mcg) during trials 008 and 009 (intent-to-treat population)

Trial 008		Trial 009	
Omlzmb	Placebo	Omlzmb	Placebo
n=268	*n=257*	*n=274*	*n=272*
570 ± 9.1	568 ± 9.2	769 ± 14	772 ± 16

Genentech also provides a summary of changes in BDP use among those who did not take medications prohibited during the core period (budesonide, celestone, soluspan, dexamethasone, fluticasone propionate, ipratropium bromide, methylprednisolone, montelukast sodium, nedocromil sodium, prednisolone, prednisolone + benzoic acid, prednisone, salmeterol hydroxynaphthoate, salmeterol, cromolyn sodium (if nasal), theophylline, triamcinolone acetonide (if inhaled), zafirlukast). The relative increase in BDP during the extension period in the omalizumab group

compared to the placebo group was slightly smaller (means change of about 70 mcg in omalizumab-treated subjects compared to 90-100 mcg in placebo-treated subjects).

CBER's sensitivity analysis of extension phase BDP use data

Because the use of BDP increased during the extension phase of the trial, CBER analyzed patterns of use in more detail. Table 61 shows the patterns of change among all extension subjects and among those with total discontinuation of use during the core period.

Table 61. Trials 008 and 009: Patterns of use of BDP during the extension phases

		Trial 008		Trial 009	
Group	Use pattern	Omalizumab	Placebo	Omalizumab	Placebo
All extension subjects		*N=243*	*N=214*	*N=252*	*N=228*
	No change	140 (58%)	97 (45%)	184 (73%)	126 (55%)
	Any increase	70 (29%)	80 (37%)	51 (20%)	78 (34%)
	Any decrease	33 (14%)	37 (17%)	17 (7%)	24 (11%)
Total discontinuers during core period		*N=103**	*N=47*	*N=117***	*N=51*
	No change	66 (64%)	27 (57%)	97 (83%)	35 (69%)
	Any increase	36 (36%)	20 (43%)	18 (15%)	16 (31%)

*1 subject with missing data
**2 subjects with missing data

Comments on BDP use data

During the 5 months of the extension period the steroid-sparing effect of active treatment was retained on average despite a small increase in use among subjects from both treatment groups. Those who discontinued totally did not contribute a greater proportion of increasers during the extension.

- *FEV_1, FVC, and FEF_{25-75}*

Trial 008

CBER's review of mean percent predicted FEV_1 values shows that this parameter remained substantially unchanged for both groups during the extension, with the difference in mean % predicted FEV_1 starting at about 7 points and varying between 2-3 points for the remainder of the trial.

Genentech reports that FVC and FEF_{25-75} were very stable. Due to the relatively stable performance of these parameters during the core period and their correlation with FEV_1, CBER did not perform a detailed review of this assertion.

Trial 009

Review of mean percents predicted FEV_1 show that this parameter remained substantially unchanged during the extension period for both groups, and that the differences were even less than in trial 008, that is, less than 2 percentage points during this phase.

Genentech states that as in trial 008, FVC and FEF_{25-75} were very stable. Due to the relatively stable performance of these parameters during the core period and their correlation with FEV_1, CBER did not perform a detailed review of this assertion.

- *Quality of life questionnaire*

Small differences between groups were noted in the proportions of subjects with ≥0.5 point improvement in scores (Appendix Table 153).

- *Missed school days/work days*

The following are stated by Genentech. They were not explored in detail. It should be noted, as in the core periods, that the comparability of the selected populations is not described in the submission. This is an issue due to the loss of subjects for analysis from the placebo group and from the school days populations in particular.

Table 62. Means (±s.d.) of missed school and work days, and unscheduled medical contacts

	Trial 008		Trial 009	
	Omalizumab	Placebo	Omalizumab	Placebo
Days missed	0.45 ± 2.34 *n=226*	0.44 ± 1.9 *n=197*	0.44 ± 3.26 *n=220*	0.40 ± 1.63 *n=198*
Days missed from school	0.40 ± 2.1 *n=40*	0.53 ± 1.84 *n=43*	0.12 ± 0.73 *n=49*	0.0 ± 0.0 *n=36*
Days missed from work	0.39 ± 1.76 *n=220*	0.33 ± 1.27 *n=192*	0.42 ± 3.26 *n=218*	0.41± 1.65 *n=194*
Unscheduled medical contacts	0.13 ± 0.44 *n=245*	0.20 ± 0.51 *n=215*	0.17 ± 0.59 *n=254*	0.21 ± 0.64 *n=229*

Comments

Results of the core period were known to sponsor personnel during the conduct of the extension phases of trials 008 and 0099. However, efforts were made to isolate the results of the core periods from investigators and subjects. The results of the extension periods are still worth examining.

Exacerbations during the extension phase remained decreased relative to placebo in omalizumab-treated subjects in the extension period. BDP use data continued to favor omalizumab in the extension phase. No notable effects were observed in spirometrically-determined measures of lung function.

BDP use data continued to favor omalizumab in the extension phase. Quality of life questionnaire results suffer from dwindling subject numbers. The data on missed school or work days also need to be viewed with caution due to lack of information on population comparability; these show no benefit of omalizumab. Unscheduled medical contact information, which also is not complete for all subjects, suggests that there is a very slight benefit of omalizumab.

Overall, the data do not show a loss of activity with omalizumab in the extension period.

Follow-up period records of asthma exacerbations

During the follow-up period trial treatment was stopped. The following exacerbation and spirometry data are reported by Genentech without detailed review by CBER; a lowered incidence of exacerbations in the formerly treated group might suggest continued efficacy. The data should be viewed with some caution because the demographic and disease characteristic comparability was not presented by Genentech.

- *Asthma exacerbations*

Asthma exacerbations were counted as investigator-assessed exacerbations, and were not qualified in terms of a protocol definition. Results were reported for the population of subjects who had a follow-up evaluation (Table 19). The data suggest that whatever benefit of omalizumab that was gained during the treatment period may be lost after cessation.

Table 63. Asthma worsenings (% of group) reported at follow-up evaluation

Trial 008	Omlzmb *n=241*	Placebo *n=230*
Asthma exacerbations	33 (14)	35 (15)
Trial 009	**Omlzmb *n=252***	**Placebo *n=235***
Asthma as adverse event	28 (11.1)	19 (8.1)

- *FEV_1, FVC, and FEF_{25-75}*

Table 64 shows that spirometry at follow-up was nearly identical between the two groups.

Table 64. Spirometry (mean ±s.d.) at follow-up evaluation

	Trial 008		Trial 009	
	Omlzmb *n=233*	Placebo *n=223*	Omlzmb *n=225*	Placebo *n=205*
FEV_1	2.46 ± 0.7	2.50 ± 0.7	2.60 ±0.8	2.60 ±0.8
FVC	3.44 ± 0.99	3.53 ± 0.97	3.76 ±1.12	3.70 ±1.06
FEF_{25-75}	1.87 ± 0.89	1.92 ± 0.89	1.95 ±1.0	1.95 ±0.99

Comments

Based upon the limited data that the follow-up provides, there is no indication of continued benefit in exacerbation rates after cessation of treatment. There was no rebound deterioration in spirometrically-determined lung function. Data interpretation is somewhat compromised by the dwindling subject numbers during the followup period.

Antibody

The antigenicity of omalizumab is discussed in a separate section of this review.

Summary: Efficacy in trials 008 and 009

- The critical efficacy trials were designed to capture relevant clinical endpoints and were performed with adequate integrity to allow firm conclusions to be drawn from them.
- Omalizumab treatment was associated with fewer exacerbations. The result was robust to data imputation sensitivity analyses. In addition, the reduction was robust to most subgroup analyses of disease severity (within the ranges of severity studied in the trials), numbers of allergens, IgE level, age, gender, and weight. There appeared to be no consistent effect in subjects with $FEV_1 \geq 80\%$ predicted. The treatment appeared more effective in females than in men.
- Larger proportions of omalizumab-treated subjects than placebo-treated subjects were able to lower or discontinue inhaled corticosteroid treatment. The steroid reduction effect was seen, by design, after several months of treatment with omalizumab. The clinical significance of this effect is not as great as a reduction from oral corticosteroid usage.
- Omalizumab effected clinically inconsequential changes in peak flow and various spirometric measures of lung function including FEV_1.
- Medical resource use was minimal and was substantially unaffected by omalizumab.
- A treatment effect was seen in the asthma symptom score and the quality of life questionnaire (which was not performed exactly as intended). The clinical meaning of the symptom score data and questionnaire data is unclear. Global evaluations, of unclear medical meaning, favored omalizumab.

- Core period results were known to at least a selected group of sponsor personnel during the conduct of the extension periods of trials 008 and 009. Despite this, results from the extension period can be viewed for potential loss of effect or greater effect. Based on relative rates of exacerbations, omalizumab remained effective over the period of the extension trial. There was some increase in corticosteroid usage during the extension phase, but the treatment advantage remained. Other clinical parameters were confirmatory of the results in the core period.
- Overall, exacerbation effects were seen in a minority of subjects in the trials, since the large majority of placebo subjects had no exacerbations in either trial.
- The subject population studied was able to be managed on modest amounts of treatment, and did not include subjects with histories of refractory asthma (such as would be evident in histories of hospitalizations or many emergency room visits), and included very few non-Caucasians or elderly subjects.

Note on the order of presentation of results

As mentioned in the summary of clinical trials, the data base contains several other trials in adolescents and adults. These will be reviewed after the review of trial 010, which was a pediatric trial. This order of presentation is chosen primarily because the design of trial 010 was very similar to that of trials 008 and 009, and presentation of its design and results here allows for easier comparison to those trials at this point.

PEDIATRIC TRIAL 010

The primary objective of trial 010 was to determine the safety of administration of omalizumab to children and adolescents. It was not powered for efficacy. However, it was a randomized, placebo-controlled trial in which many of the same efficacy parameters were collected as in trials 008 and 009.

Title

Trial 010 was entitled, "A Phase III, 7-month double-blind, randomized, parallel-group, placebo-controlled, multicenter trial with a 5-month open-label extension period to assess safety and tolerability, steroid-reduction, pharmacokinetics, and pharmacodynamics of subcutaneous rhuMAb-E25 in children (6-12 years) with allergic asthma requiring daily treatment with inhaled corticosteroids."

Dates of the protocol

The protocol was made final on November 21, 1997 and amended formally on May 7, 1998. This review reflects the final amended version of the protocol.

Design

This was a year-long trial with a planned enrollment of 324 subjects whose design was similar to trial 008 and 009, with the following major exceptions:

- The trial was not powered to develop statistical significance on an exacerbation outcome; rather, it was designed to examine safety and tolerability.
- Subjects were to be 6-12 years old
- Subjects were to be on chronic corticosteroid at baseline but were not required to have symptoms or to have a decreased FEV_1
- In the extension phase, subjects were all to be on active treatment, that is, placebo subjects were to be switched to omalizumab
- Randomization to omalizumab or placebo was 2:1

Management of corticosteroid dosing (including programmed reductions) and recognition and treatment of asthma exacerbations were central to this trial and were performed as in trials 008 and 009.

Objectives

The objectives of the trial were to examine efficacy, safety, and pharmacokinetics and pharmacodynamics of omalizumab.

Trial treatments

The same product was used for trial 010 as was used for trials 008 and 009.

A chart was used for dosing (Table 65), with the same rules as in trial 008. However, because body masses could be much lower, serum IgE could be much higher before a limiting dose was reached.

Table 65. Dosing table for trial 010

Baseline IgE (IU/mL)	Milligrams (mg) Per Dose: Body weight (kg) 20-30	>30-40	>40-50	>50-60	>60-70	>70-90	Frequency of Dosing
>30-100	150	150	150	150	150	150	Q4wk
>100-200	150	150	300	300	300	300	
>200-300	150	300	300	300	225	225	Q2wk
>300-400	300	300	225	225	225	300	
>400-500	300	225	225	300	300	375	
>500-600	300	225	300	300	375		Not Dosed
>600-700	225	225	300	375			
>700-800	225	300	375				
>800-900	225	300	375				
>900-1000	300	375					
>1000-1100	300	375					
>1100-1200	300						
>1200-1300	375						

Concomitant medications

Guidelines for the use of corticosteroid, albuterol rescue, and other concomitant treatments were the same as those for trials 008 and 009.

Subject qualifications

The differences from the subject inclusion and exclusion criteria for trials 008 and 009 are listed below. The inclusion criteria were different from those of trials 008 and 009 in that they stipulated the following:

--Total serum IgE level ≥30 IU/ml and ≤1300 IU/ml and body weight ≤90 kg.

--Baseline FEV_1 ≥60% of the predicted normal value for the patient.

--no minimal criterion was set for the daily symptom score; rather, subjects were to be well controlled, defined as:

· minimal asthma symptoms during the day

· night-time awakening due to asthma symptoms < 1 time a week

· minimal limitations on normal activities and exercise

· β-agonist requirement, on average, not exceeding 4 puffs of albuterol (90 mg/puff) or its equivalent

· PEFR variability (difference between PM and AM value) < 20 %

· minimal or no side effects from medication

--Required treatment with corticosteroid was to be equivalent to BDP, ≥168 to 420 mg/day

Exclusion criteria were not substantively different from those of trials 008 and 009.

Comments

Because body masses were expected to be lower in children, and because the limit of dosing depended upon the product of mass and serum IgE, the upper limit of IgE was higher than in trials 008 and 009. Since the primary objective of the trial was to obtain safety data, subjects for

this trial could have very minimal to no symptoms or impairment in baseline FEV_1. Required corticosteroid dosing at baseline was consistent with pediatric dosing.

Procedures and evaluations

Procedures were substantially the same as in trials 008 and 009; serum pregnancy testing was omitted.

Analytical plan

The analytical methods were the same as in trials 008 and 009, with somewhat different organization of endpoints, as the primary objective was safety information.

Endpoints

- Primary endpoints were defined during the steroid reduction period only:
  1. Proportion of subjects with successful reduction (≥50% dose reduction) of the dose of BDP
  2. Proportion of subjects with complete withdrawal (100% dose reduction) of the dose of BDP
  3. Percent reduction in the dose of BDP
- Exploratory endpoints defined for the steroid stabilization period
  1. Number of patients experiencing at least one asthma exacerbation
  2. Number of asthma exacerbation episodes experienced per patient
  3. "Asthma-free" days

     An "asthma-free" day was a low-symptom day, defined as the treatment day when all of the following criteria are met:

     · AM PEFR ≥80% of baseline (mean last 14 days prior to randomization)

     · Daytime asthma score ≤1

     · Nighttime asthma score =0

     · Rescue medication use ≤2 puffs
  4. Morning PEFR
  5. FEV_1
  6. FVC
  7. FEF_{25-75}
  8. Nocturnal asthma symptom score
  9. Presence/absence of morning asthma score
  10. Daytime asthma symptom score
  11. Number of puffs of rescue medication taken daily
- Exploratory endpoints defined for the steroid reduction period
  1. Number of subjects experiencing at least one asthma exacerbation
  2. Number of asthma exacerbation episodes experienced per subject
  3. Patient's and investigator's global evaluation of treatment effectiveness

Summary of statistical methods for primary endpoint

The statistical analytical methods, including the sample analytical populations, were the same as those for trials 008 and 009. The sample size was not based upon statistical considerations.

Protocol modifications

Like trials 008 and 009, the protocol was made final on November 21, 1997. The following changes were made:

1. There was one formal protocol amendment, dated May 7, 1998. This provided for the following:
   - collection of venous blood and urine at Visit 5 (Week 8, steroid stabilization period) and at Visit 15 (Week 36, extension period) and for laboratory safety assessments, measurement of

height and weight, spirometry, and recording of concomitant medications, adverse events, and asthma exacerbations during the follow-up period.

- A clarification was made that the persons preparing or administering the trial agent were not be involved in subject evaluations and added spirometric measurements at visit 20.

2. A substudy was conducted at two of the participating centers to evaluate the effects of omalizumab on exhaled oral and nasal nitric oxide.

Comments

Although it was not sized for efficacy like trials 008 and 009, trial 010 had adequate duration and appropriate endpoints to collect clinically meaningful data. The protocol intentionally selected subjects with asthma that was well-managed on modest amounts of medication. Changes made to the protocol after it was implemented would be expected to have no appreciable impact on the results of the trial.

Results of the substudy on nitric oxide were not presented, but are not critical to the assessment of the clinical results.

Results: Conduct of the trial

Dates of the trial

The first subject was recruited into the trial on February 12, 1998. The last subject completed the trial on January 10, 2000.

Screening failures

Of 501 persons screened for entry into the trial, 1/3 were deemed ineligible (167/501). Reasons were diverse; the 4 major exclusionary reasons were: IgE >1300, 34 persons (7%), IgE <30, 27 persons (5%), reversibility of airflow obstruction <12%, 25 persons (5%), and skin test negative, 23 persons (5%). Thirteen (2.6%) were screened out for having a combination of IgE and body mass outside the dosing table limits. An "other" category accounted for 25 persons (5%).

Enrollment by site

There were 27 sites in trial 010 (Table 66). No single site dominated enrollment.

Table 66. Trial 010: Enrollment by site

Number of subjects/site	Number of sites
6-10	9
11-15	12
17-23	6

Demographics and baseline characteristics

Table 67 shows that the baseline demographic characteristics were well balanced. Under the age of 10, boys are more likely as girls to develop asthma, so the preponderance of males in this trial is not surprising. Compared to trials 008 and 009 a slightly higher proportion of both groups was non-Caucasian. In contrast to trial 008 and 009, FEV_1 for all subjects was in the normal range, but there were more visits for medical care in this pediatric population. This may reflect an earlier threshold for seeking medical care for children.

Table 67. Trial 010: Demographics and baseline characteristics

	Omalizumab *n=225* (%)	Placebo *n=109* (%)
Sex, N (%) Male Female	 158 (70.2) 67 (29.8)	 73 (67.0) 36 (33.0)
Race, N (%) Caucasian Black Other	 168 (74.7) 38 (16.9) 19 (8.4)	 86 (78.9) 14 (12.8) 9 (8.3)
Mean Age, year (range)	9.4 (5-12)	9.5 (6-12)
Mean duration of asthma, year (range)	6.1 (1-12)	6.1 (1-12)
Mean BDP dose, mcg/day (range)	284 (168-672)	267 (168-504)
Mean serum total IgE, IU/ml (range)	348 (20-1269)	323 (29-1212)
Mean serum total IgE, IU/ml by treatment schedule	Q2w: 640 Q4w: 198	Q2w: 646 Q4w: 171
Mean FEV_1, % predicted (range)	84 (49-129)	85 (43-116)
Mean qualifying FEV_1 reversibility, (%)	20.39	19.59
Hospitalization for asthma treatment past year, N (%)	18 (8.0)	9 (8.0)
Mean emergency room visit for asthma past year	0.6	0.6
Mean doctor's office visits for urgent asthma treatment past year	1.9	1.6

Premature discontinuations

[This reviewer is indebted to Dr. Dwaine Rieves, CBER for the organization of data as presented in Table 68.]

Table 68 shows the numbers of subjects who completed trial 010. As in trials 008 and 009, premature discontinuations during the core period were close to 10%, and were greater in the placebo group. Consent withdrawal was the most frequent reason for failure to complete the core period; reasons were diverse for both groups. There was no imbalance in the numbers discontinuing due to unsatisfactory therapeutic effect, as was seen in trials 008 and 009, probably due to the relatively well nature of the subjects. During the extension, while all subjects received omalizumab, administrative problems were the most frequently cited reason for discontinuation.

Table 68. Trial 010: Subjects prematurely discontinued *n* (%)

Total no. patients, n (%)	Omalizumab	Placebo
Double blind 7 months core period		
Randomized	225	109
Competed stabilization	216 (96%)	101 (93%)
Completed steroid reduction	209 (93%)	97 (89%)
Discontinued	16 (7%)	12 (11%)
due to AE	1 (<1%)	1 (<1%)
due to unsatisfactory therapy	1 (<1%)	1 (<1%)
due to protocol violation	1 (<1%)	2 (2%)
due to consent withdrawal	7 (3%)	5 (5%)
due to administrative problem	3 (1%)	3 (3%)
lost to follow-up	3 (1%)	0
Double blind 5 month extension period (all patients received omalizumab)		
Completed core study but did not enter extension study	0	
Entered into extension	309 (93%)	
Completed extension	298 (89%)	
Discontinued	11 (3%)	
due to consent withdrawal	1 (<1%)	
due to lost to follow-up	1 (<1%)	
due to administrative problems	9 (3%)	
Three month no treatment follow-up period		
Provided any follow-up data	206 (92%)	98 (90%)
Completed extension and completed follow-up period	194 (86%)	90 (83%)
Discontinued from extension period but completed follow-up period	5 (2%)	1 (<1%)
Completed core period, did not enter extension but completed follow-up period	0	0
Discontinued from core period but completed follow-up period	0	2 (2%)
No final follow-up visit	19 (8%)	11 (10%)

Eligibility and other protocol violations

Table 69 shows relatively frequent or important protocol violations in trial 010. Other violations were rarer than those listed.

Table 69. Trial 010: Most common important protocol violations (Proportion of subjects affected*)

Violation	Omlzmb *N=225*	Placebo *N=109*
Run-in period <4 weeks	35 (16)	19 (17)
Change in BDP maintenance dose of 50% or more for greater than 28 days	16 (7.1)	4 (3.7)
Baseline BDP dose greater than 10 puffs	11 (4.9)	5 (4.6)
Reduced BDP dose in last 4 weeks of reduction period	9 (4.0)	6 (4.4)
Run in period stable BDP dose <4 weeks	5 (2.2)	3 (2.8)
Excluded concomitant med.	5 (2.2)	2 (1.8)
Baseline serum IgE <30	5 (2.2)	1 (0.9)
Dosing error (missed or extra dose)	5**	1**
FEV_1% <60%	6 (2.7)	0 (0)

*protocol violations not listed by subject in submission; calculated by CBER when likely to be single occurrence
**possible multiple occurrences; incidence by subject not calculated by CBER

Comments

Run-in period violations were common but were balanced between arms. As stated in the comments for run-in violations for trials 008 and 009, this would have had the effect of increasing variability, but would not have had a definite biasing effect in the trial.

Changes in dosing of BDP or violations of inclusion criteria for BDP dosing were uncommon and reasonably balanced.

Excluded concomitant medication, serum IgE, missed or extra dose, and FEV_1 criteria violations were uncommon, and would not be expected to affect an assessment of efficacy notably.

In summary, protocol violations were of minor nature and would not have been expected to render the results of the trial uninterpretable.

Data base issues

- *Changes to the data base after data lock*

Upon request, Genentech supplied a detailed listing of changes that were made to the data base after it was unblinded. During the core period no exacerbations were added or deleted from the data base (6 concomitant medication records and 1 hospitalization record were changed). During the extension period, records were modified for 1 exacerbation (in addition, 11 concomitant medication, 4 adverse event, 1 discontinuation, and 1 outpatient visit records were modified). The changes to the exacerbation data are very minor with respect to efficacy conclusions.

- *Transcription of medication data pertaining to exacerbations*

As for the adult trials, some medication data pertaining to asthma exacerbations were not recorded on asthma exacerbation forms (medication reported in full on the exacerbation report form for omalizumab and placebo was 88.6% and 89.3% of records, respectively). Review of the data submitted upon request by Genentech does not show an irregularity in the correction of asthma exacerbation medication data.

- *Transcription of exacerbation classification data*

CBER compared data tabulations with classifications of exacerbations as represented in the case report forms of 18 subjects (about 24 records). No misrepresentations were detected.

Comments

Changes to the efficacy data after unblinding appear to have been minor.

Completeness of data collection

As for the adult trials, CBER examined diary and spirometry data (symptoms, medication usage, and FEV_1 and FVC, respectively) files. For diary data, the submission included raw data for the core period only (not the extension or follow-up periods). Raw spirometry data were included for the core, extension, and follow-up periods. As a proportion of diary entries for the core period, missing diary data averaged between 5-7% (2 evening parameters, evening peak expiratory flow and evening rescue medication were not provided by 87%of subjects, however); spirometry, which was conducted by trial personnel, was a little better; missing FEV_1 and FVC data was 3% and 5%, respectively. Exacerbation data were collected on forms filled out when an event occurred, and not on a fixed schedule, rendering completeness of collection of these data difficult to assess.

Data collection was very good in this trial.

Comment

In summary, the conduct of the trial was good, and will allow a review of efficacy data as presented.

Results: Efficacy

Analytical populations

As in trials 008 and 009, all subjects received at least one dose, and thus qualified for The protocol's definition of an "intent-to-treat" population, which was the primary population for analysis.

Primary endpoint

Table 70 shows summary statistics on numbers of subjects and proportions in each group with given reductions in the corticosteroid usage from baseline (visit 3) to the end of the double-blind phase. As in trials 008 and 009, Genentech attributed 0% reduction to those who did not enter the steroid reduction phase, and calculated a percent reduction corresponding to the last dose in the steroid reduction phase prior to discontinuation for those who discontinued prematurely. The p-value using the CMH test stratified by treatment schedule was 0.001. The median percent reduction was 100% for omalizumab -treated subjects and 67% for placebo-treated subjects.

Table 70. Trial 010: Reductions in BDP dosing (intent-to-treat analysis, with imputations)

Percent reduction in BDP	Q2w		Q4w		Overall	
	Omalizumab *n=76*	Placebo *n=35*	Omalizumab *n=149*	Placebo *n=74*	Omalizumab *n=225*	Placebo *n=109*
100%	*36 (47%)*	*7 (20%)*	*88 (59%)*	*35 (47%)*	*124 (55%)*	*42 (39%)*
75% to ≤100%	44 (57.9%)	9 (25.7%)	103 (69.1%)	45 (60.8%)	147 (65.3%)	54 (49.5%)
50% to < 75%	18 (23.7%)	8 (22.9%)	16 (10.7%)	11 (14.9%)	34 (15.1%)	19 (17.4%)
25% to < 50%	4 (5.3%)	8 (22.9%)	11 (7.4%)	7 (9.5%)	15 (6.7%)	15 (13.8%)
0% to < 25%	10 (13.2%)	10 (28.6%)	18 (12.1%)	10 (13.5%)	28 (12.4%)	20 (18.3%)
0%	9 (12%)	9 (26%)	17 (11%)	9 (12%)	26 (12%)	18 (17%)
< 0%	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (1.4%)	1 (0.4%)	1 (0.9%)

Comments

The large number of discontinuations and partial discontinuations from corticosteroids in both treatment arms suggests that at baseline a large proportion of subjects overall were treated with more BDP than needed. However, discontinuations from corticosteroids were more frequent in the omalizumab group, regardless of treatment schedule.

CBER's sensitivity analysis of the primary endpoint

CBER calculated the numbers of subjects with complete withdrawal of corticosteroid dosing during the steroid reduction phase, as a function of the dose they were on at the visit 3 baseline (Table 71). As in trials 008 and 009, discontinuations from corticosteroids in the omalizumab group were not restricted to subjects taking low baseline doses, but were distributed among the subjects, including those in the highest BDP use.

Table 71. Numbers (% of group) with 100% reduction in BDP dosing, by baseline dose of BDP

Baseline BDP dose (μg/day)	Omalizumab	Placebo
168	51/70 (73)	22/40 (55)
252	21/34 (62)	6/19 (32)
336	39/86 (45)	9/34 (26)
420	9/26 (35)	3/10 (30)
*Subject totals**	*216*	*103*

*Totals less than total enrolled, since table shows only dosing groups with adequate subjects for comparisons

Submitted subset analyses of primary endpoint

Table 72 shows submitted analysis of corticosteroid reductions of ≥75% of baseline use by subgroups of sex, race, age, and FEV_1 as a marker for disease extent. Data from the ethnic groups "Oriental" and "Other" and from low percent predicted FEV_1 subjects are too sparse for conclusions to be drawn. There appeared to be no gender effect nor an effect of age within this trial's narrow age range.

Table 72. Trial 010: Corticosteroid reductions of ³ 75%, number of subjects (% per group), with imputations

Subgroup			Omalizumab	Placebo
Ethnicity	White	*n*	*168*	*85*
			115 (69)	43 (51)
	Black	*n*	*38*	*14*
			23 (61)	7 (50)
	Oriental	*n*	*3*	*0*
			0	0
	Other	*n*	*16*	9
			9 (56)	4 (44)
FEV_1	>65%	*n*	*204*	*103*
			140 (69)	52 (51)
	<65%	*n*	*21*	*5*
			7 (33)	2 (40)
Sex	Male	*n*	*158*	*73*
			102 (65)	37 (51)
	Female	*n*	*67*	*35*
			45 (67)	17 (49)
Age	5-9	*n*	*106*	*49*
			70 (66)	21 (43)
	10-12	*n*	*119*	*60*
			77 (65)	33 (55)

Analysis of potential unblinding of subjects or investigators

As for the adult trials, CBER examined injection site reactions as an indication of potential biasing of subjects or investigators (Table 73). The proportions of subjects with any injection site reaction were almost exactly equal, and the proportions of subjects with between visit symptoms or moderate-severe injection site reactions were approximately equal. In both trials, slightly greater proportions of subjects reported any symptom between a visit (a longer reaction), but the proportions of moderate-severe burning, itching, and hives were similar.

Table 73. Trial 010: Subjects (% of group) with injection site reactions

	Omlzmb *n=225*	Placebo *n=109*
Any symptom	224 (100)	109 (100)
Between visit symptom	97 (43)	49 (45)
Moderate-severe		
burning	14 (6)	9 (8)
itching	15 (7)	12 (11)
hives	1 (0)	1 (1)

Comment

Injection site reactions were balanced and not likely to affect differentially the perception of what treatment subjects were on, and therefore would not be likely to have affected the outcome of the trial substantially.

Exploratory endpoints

- *Number of asthma exacerbations*

As in trials 008 and 009, the primary analysis imputed exacerbations to those who discontinued prematurely. Table 74 shows exacerbations during the stable steroid phase, as determined using the protocol-defined technique of imputation. There was no statistical difference between the two treatment arms (p=0.093). However, the treatment effect size was comparable to that seen in trials 008 and 009. Both treatment schedules contributed to the effect.

Table 74. Trial 010: Asthma exacerbations in stable steroid phase (subjects, %)*

Number of exacerbations	Q2w		Q4w		overall	
	Omlzmb *n=76*	Placebo *n=35*	Omlzmb *n=149*	Placebo *n=74*	Omlzmb *n=225*	Placebo *n=109*
0	61 *(80%)*	26 *(74%)*	129 *(87%)*	58 *(78%)*	190 *(84%)*	84 *(77%)*
1	12 *(16%)*	6 *(17%)*	13 *(9%)*	11 *(15%)*	25 *(11%)*	17 *(16%)*
total ≥1	15 *(20%)*	9 *(26%)*	20 *(14%)*	16 *(22%)*	35 *(16%)*	25 *(23%)*

*ITT population; imputation according to protocol

Table 75 shows the numbers and proportions of protocol-defined asthma exacerbations during the steroid reduction phase. During this phase, the treatment effect was greater than that in trials 008 and 009. The p-value using CMH stratified by treatment center was <0.001.

Table 75. Trial 010: Asthma exacerbations in steroid reduction phase (subjects, %)*

Number of exacerbations	Q2w		Q4w		overall	
	Omlzmb *n=76*	Placebo *n=35*	Omlzmb *n=149*	Placebo *n=74*	Omlzmb *n=225*	Placebo *n=109*
0	63 *(83%)*	17 *(49%))*	121 *(81%)*	50 *(68%)*	184 *(82%)*	67 *(62%)*
1	7 *(9%)*	9 *(26%)*	11 *(7%)*	16 *(22%)*	18 *(8.0%)*	25 *(23%)*
total ≥1	13 *(17%)*	18 *(51%)*	28 *(19%)*	24 *(32%)*	41 *(18%)*	42 *(39%)*

*ITT population; imputation according to protocol

Comments

As in trials 008 and 009 there were few exacerbations overall, which is not surprising in this trial since the subjects were enrolled relatively well. There were twice as many subjects in the Q4w schedule as in the Q2w schedule, so the majority of the data in the overall group results was attributable to that schedule; treatment schedule had no noticeable effect on differential efficacy of product over placebo. There was remarkably more advantage of omalizumab over placebo during the steroid reduction phase, a pattern that wasn't noted in trials 008 and 009. This may have been due to more aggressive withdrawal from corticosteroids, as evidenced in the higher proportions of subjects withdrawn from these agents in this trial. The placebo proportion of subjects with ³1 exacerbation was higher in trial 010 than in trials 008 and 009.

Sensitivity analyses

Observed exacerbations

As in trials 008 and 009, most subjects did not have any exacerbations. The analysis of subjects with observed exacerbations in both the stable steroid and steroid reduction phases was consistent with the analysis per protocol (Appendix Table 154 and Table 155).

Summary of different imputation analyses

Table 76 shows the results of the statistical tests performed by Genentech on the intent-to-treat population, and displays mean exacerbation counts for each phase.

Table 76. Trial 010: Mean exacerbations per subject and p-value using different imputation techniques

Imputation Method	Stable steroid phase			Steroid reduction phase		
	Omlzmb	Placebo	*p-value*	Omlzmb	Placebo	*p-value*
Protocol	0.30	0.40	*0.093*	0.42	0.72	*<0.001*
Observed (no imputations)	0.15	0.22	*0.148*	0.16	0.34	*<0.001*
Single	0.18	0.29	*0.034*	0.22	0.44	*<0.001*
Maximum	0.26	0.44	*0.031*	0.36	0.66	*<0.001*

Comments

During the stable steroid phase, alternative imputation techniques resulted in different estimates of the treatment effect, some higher, and some lower than the protocol-specified technique. During steroid reduction, the intertreatment difference was not changed using the maximum observed imputation technique, but was lowered in the other two methods. In sum, there was a treatment effect of omalizumab, regardless of the imputation technique.

Analysis of intensity of steroids used for exacerbations

The majority of exacerbations qualified on the basis of use of oral corticosteroids as in trials 008 and 009 (Table 77).

Table 77. Maximal intensity of corticosteroid dosing for protocol-defined exacerbations

	Stable steroid		Steroid reduction	
	Omalizumab	Placebo	Omalizumab	Placebo
Doubling inhaled	9 27%	1 4%	3 9%	2 5%
Oral	20 61%	22 92%	32 91%	33 90%
IV	4 12%	1 4%	0 0%	2 5%
TOTAL	33 100%	24 100%	35 100%	37 100%

Comments

Numbers of exacerbations were small, so this analysis contributes only a small degree. However, there does not appear to be a notable difference in the intensity of corticosteroid dosing for exacerbations that occurred in the treatment arms, suggesting that the lowered number of exacerbations in the active arm was not due to elimination of only the mild exacerbations.

CBER's sensitivity analyses of exacerbations and duration of effect

Analysis of effect by site

CBER examined the treatment effect by site, calculated as the proportion of subjects with ≥1 exacerbation, using observed counts (Table 78). In the table, a negative value signifies that the

proportion of subjects in a treatment group with ≥1 exacerbation were lower in placebo; a positive value indicates a benefit of omalizumab.

Table 78. Numbers of sites in categories of intertreatment differences in proportions of subjects with exacerbations (placebo- omalizumab)

	Difference in proportions of subjects with ≥1 exacerbation (Placebo-Omalizumab)	All sites	Larger sites (n≥15)
Stable Steroid phase	(-)	10	1
	0	6	1
	(+)	11	5
Steroid reduction phase	(-)	3	1
	0	5	0
	(+)	19	6

*for sites of ≥12

Comments

The numbers of sites reporting a (+) difference in the proportions of successes as determined by the numbers of subjects with ³1 were in the majority in the steroid reduction phase, but not in the steroid stabilization phase. Most of the largest sites had a positive treatment effect, but the numbers of these sites is very small. These results corroborate the lack of statistical treatment difference in the stabilization phase.

Analysis of the duration of effect

CBER examined the risk of protocol-defined exacerbations as a function of time in the trial for individual subjects (Table 79). In this analysis, all subjects who enter a time interval are counted for that interval. This analysis shows that there is no diminution in the effect of omalizumab over the duration of the core period.

Table 79.Trial 010: Risk of exacerbations by treatment group over core period

Interval of trial (days)	Omalizumab		Placebo		Relative Risk (Omlzmb / Placebo)
	Subjects at risk	Exacerbations/ subject	Subjects at risk	Exacerbations/ subject	
0-29	225	0.044	109	0.073	0.61
30-59	222	0.050	108	0.083	0.59
60-89	221	0.041	106	0.047	0.86
90-119	219	0.037	104	0.029	1.27
120-149	217	0.046	102	0.118	0.39
150-179	214	0.047	101	0.139	0.34
180-209	210	0.043	100	0.100	0.43
210-239	20	0.000	9	0.000	-
316-317	0	-	2	0.000	-

Analysis of effect by corrected nominal dose

As for trials 008 and 009, CBER correlated a measure of efficacy, the proportions of subjects with ≥1 exacerbation, as a function of corrected nominal monthly dose per kilogram of subject mass. Nominal dose was corrected for baseline subject body mass and IgE. In trial 010, corrected nominal monthly dose varied from 0.017 mg/kg/IU (IgE/ml) to 0.25 mg/kg/IU (IgE)/ml. Subject numbers at the extremes of dosing were very small in the placebo group, so conclusions about these extremes are impossible to make. Within the limitations of the data, there is no evidence for a loss of

effectiveness at lower doses. Table 80 shows that within the limitations of the data, there is no evidence for a loss of effectiveness at lower doses.

Table 80. Trial 010: Numbers and proportions of subjects with ³1 exacerbation, by monthly dose actually received

		Stable steroid		Steroid reduction	
monthly mg/[kg x IgE]		Omalizumab	Placebo	Omalizumab	Placebo
0.01 to <0.02	*n*	*8*	*4*	*8*	*4*
		2 (25)	0 (0)	2 (25)	0 (0)
0.02 to <0.03	*n*	*20*	*7*	*20*	*7*
		3 (15)	0 (0)	0 (0)	2 (29)
0.03 to <0.05	*n*	*107*	*49*	*107*	*49*
		15 (14)	14 (29)	15 (14)	19 (39)
0.05 to <0.07	*n*	*68*	*39*	*68*	*39*
		7(10)	5 (13)	5 (7)	10 (26)
0.07 to <0.11	*n*	*16*	*8*	*16*	*8*
		1 (6)	1 (13)	2 (13)	0 (0)
>=0.11	*n*	*6*	*2*	*6*	*2*
		0 (0)	0 (0)	3 (50)	0 (0)
total n		*225*	*109*	*225*	*109*

Submitted subset analyses of exacerbations

Table 81 shows a categorization of exacerbation counts (including imputations) into numbers of subjects with 0 or ≥1 exacerbation, by subgroups of ethnicity, age, sex, and FEV_1. These analyses do not show a subgroup with a clear loss of efficacy. Numbers of subjects in the "Black" and low FEV_1 category make the apparent lack of effect in these subgroups during the steroid stabilization period uncertain. Although these data show that the proportions of males with ≥1 exacerbation were not different between the treatment groups, their mean exacerbation count favored omalizumab (data not shown), and the difference favored omalizumab in the steroid reduction phase.

Table 81. Trial 010: Protocol-defined exacerbations by subgroup, *including imputations* (% per group)

Subgroup			Stable steroid phase		Steroid reduction phase	
			Omalizumab	Placebo	Omalizumab	Placebo
Ethnicity	White	*n*	*168*	*86*	*168*	*86*
		≥1	22 (13)	33 (22)	23 (14)	30 (35)
	Black	*n*	*38*	*14*	*38*	*14*
		≥1	8 (21)	2 (14)	14 (37)	8 (57)
	Oriental	*n*	*3*	*0*	*3*	*0*
		≥1	1	0	2	0
	Other	*n*	*16*	*9*	*16*	*9*
		≥1	4 (25)	4 (44)	2 (12)	4 (44)
FEV_1	>65%	*n*	*204*	*103*	*204*	*103*
		≥1	28 (14)	21 (23)	33 (16)	39 (38)
	<65%	*n*	*21*	*6*	*21*	*6*
		≥1	7 (33)	1 (17)	8 (38)	3 (50)
Sex	Male	*n*	*158*	*73*	*158*	*73*
		≥1	29 (18)	13 (18)	32 (20)	28 (38)
	Female	*n*	*67*	*36*	*67*	*36*
		≥1	6 (9)	12 (33)	9 (13)	14 (39)
Age	5-9	*n*	*106*	*49*	*106*	*49*
		≥1	17 (16)	10 (20)	21 (20)	24 (49)
	10-12	*n*	*119*	*60*	*119*	*60*
		≥1	18 (15)	15 (25)	20 (17)	18 (30)

CBER's subset analyses of exacerbations

Using the observed exacerbation data base, CBER performed an analysis of efficacy by surrogates of severity (doctor's visits, and quartiles of baseline BDP usage, and IgE), numbers of allergens to which subjects were sensitive, weight, and age (see Appendix Table 156 through Table 163). The analysis of efficacy by baseline IgE is especially important due to the wide range of IgE that is seen in this trial. These analyses do not show a pattern of loss of effect at extremes of age, weight, or allergen sensitivity, baseline IgE, or disease severity.

Comments

Subgroup analyses do not show concerning patterns in subgroups of age, disease characteristics, allergy characteristics, age, or gender. Data on ethnicities other than "White" are too sparse to justify conclusions.

- *Number of subjects with ³1 asthma exacerbation*

This can be gleaned from Table 74 and Table 75 The statistical test revealed a trend in favor of treatment during the stable steroid phase (p=0.095), and a statistically significant difference during the steroid reduction phase (p<0.001).

- *"Asthma-free" days*

As noted in the review of trials 008 and 009, this term is a misnomer in that it allows for some daytime symptoms and the daily use of 2 puffs of albuterol rescue medication. (As in trials 008 and 009, while the protocol specified that the PEFR should be ≥80% of best, Genentech analyzed the data using a more stringent PEFR criterion of ≥90%.). The median proportion of low-symptom days in the omalizumab group was 0.72 compared with 0.65 in the placebo group. Genentech does not report inferential statistics. The results show a slight advantage of omalizumab over placebo.

Table 82. Proportions of low symptom days

Proportion of low symptom days	Omalizumab *n=224*	Placebo *n=109*
80% to <=100%	89 (39.7%)	33 (30.3%)
60% to < 80%	48 (21.4%)	27 (24.8%)
40% to < 60%	35 (15.6%)	15 (13.8%)
20% to < 40%	19 (8.5%)	17 (15.6%)
0% to < 20%	33 (14.7%)	17 (15.6%)

- *Morning PEFR; FEV_1; FVC; FEF_{25-75}*

Mean PEFR in the omalizumab group was 261 l/min, in placebo, 264 l/min. Mean PEFR improved slightly in the omalizumab group to 270 l/min but stayed essentially the same in the placebo group at 265 l/min. These differences were slight and clinically insignificant; Genentech did not report statistics on the differences.

Mean FEV_1 was 1.80 l/min and 1.86 l/min in the omalizumab and placebo groups, respectively, at baseline. At the end of the core period values were virtually the same at 1.89 l/min and 1.88 l/min.

Mean FVC was 2.27 and 2.33 l/min in the omalizumab and placebo groups at baseline, respectively, and end of core period values were virtually identical at 2.41 and 2.42, respectively.

Mean FEF_{25-75} was 1.72 l/min and 1.75 l/min in the omalizumab and placebo groups at baseline, respectively. This parameter stayed stable in the active group but declined to a small extent in the placebo group during the trial: end of core period values were 1.78 l/min and 1.69 l/min, respectively. These differences were very small and of little clinical significance.

Comments

As Genentech reports, there was little change in these parameters over time and minimal differences between the two treatment groups. Overall, these data provide no support for the adult data, nor do they cause a concern for the product in the pediatric group.

- *Mean nocturnal asthma symptom score; mean morning asthma symptom score; mean daytime asthma symptom score*

Medians of the mean nocturnal asthma symptom score remained at 0 for both treatment arms during the core period. Means for the active treatment group were very slightly lower (less than 0.1 units) than in the placebo group for most visits of the trial.

Medians of the mean nocturnal asthma symptom score remained at 0 for most visits in both treatment arms during the core period, and the pattern of the mean scores was similar to that of the nocturnal scores.

Medians of the mean daytime asthma symptom score favored the active treatment group, but the differences were small, up to 0.21 units. Mean scores paralleled medians, with the maximal difference in group means of 0.18 units.

Comments

Asthma symptom scores were very low at baseline and showed slight treatment effects or none.

- *Number of puffs of albuterol rescue medication*

Medians of the mean daily puffs at baseline were very small (0.31 active, 0.43 placebo) consistent with the low severity of baseline disease in the trial population. During the trial, median usage in the placebo group remained the same, while use in the omalizumab group fell to between 0 and 0.1-0.2 puffs daily at the end of the trial.

Comments

Usage of rescue medication was very low at baseline, and the magnitude of the treatment effect noted at the end of the trial was clinically insignificant.

Global evaluation of treatment effectiveness at the end of the reduction phase

Proportions of subjects with global ratings of excellent, good, moderate, poor, and worsening of asthma (Appendix Table 164) favored omalizumab and paralleled those in trials 008 and 009.

Comments on exploratory endpoints

Exacerbation data were consistent with trials 008 and 009 in showing a benefit of omalizumab, but differed from these trials in showing an appreciably larger intertreatment difference during the steroid reduction phase. Physiological measures, medication use data, and symptom score data reflected the mild disease of these children, showing little effect.

Other variables

- *Pediatric Juniper quality of life questionnaire*

As in the adult trials, some subjects did not follow the intended plan for a subsection of the activities domain (in the pediatric version of the questionnaire 3 activities were to be specified). The following analyses are reported as presented, without additional analysis by CBER. The between-treatment analysis was an analysis of covariance including treatment, center, and treatment schedule as factors, with a "centered" baseline as a covariate.

Genentech does not present summary statistics on proportions of subjects in the steroid stabilization phase who achieved improvements of ≥0.5 from baseline, but states that no significant differences were seen between the treatment groups in any of the domains (activities, emotions, symptoms, and overall. CBER did not examine these assertions.

During the steroid reduction phase, Genentech reports that no statistical difference was seen between treatment groups in the activities domain when the 3 specified activities were excluded (median change of 0 for either group), but that if the activities were included, there was a statistically significant difference (p=0.036 (p=0.046 with last observation carried forward technique), with a median change of 0.5 in the omalizumab-treated group, and 0.2 in the placebo group). Subject numbers used in the analyses are not reported.

In the analysis of the emotions domain, no statistical difference between the treatment groups was reported (with a median value of change from baseline of 0.4 in omalizumab-treated subjects and 0.1 in the placebo group). Subject numbers used in the analyses are not reported.

A statistically significant difference (p=0.016, p=0.044 using the last observation carried forward technique) was reported, with a median change from baseline of 0.3 in the omalizumab-treated group, 0.1 in the placebo-treated group. Subject numbers used in the analyses are not reported.

- *Subjects' missed school days due to asthma*

  Based upon an overall subject number of 223 in the omalizumab-treated group and 109 in the placebo-treated group, median missed days of school were 0 for both groups, with means (± std. dev.) of 0.6 ± 1.9 and 1.2 ± 3.3, respectively. No statistics are reported.

- *Caregiver's missed work days due to asthma*

  Based upon an overall subject number of 196 in the omalizumab-treated group, and 93 in the placebo-treated group, median missed days of work for caregivers were 0 for both groups, with means (± std. dev.) of 0.3 ± 1.5 and 0.5 ± 2.3, respectively. No statistics are reported.

- *Unscheduled medical contacts*

Table 83 shows Genentech's analysis of the numbers of unscheduled medical contacts for the entire treatment period. Omalizumab was associated with a slightly lower number of mean visits, more pronounced during steroid reduction, with no effect on the median number of contacts.

Table 83. Trial 010: Mean (±std. dev.) unscheduled medical contacts (intent-to-treat population*)

		Omalizumab	Placebo
Stable steroid phase	*n* mean ±s dev median	*225* 0.13 ± 0.52 0	*109* 0.23 ± 0.74 0
Steroid reduction phase	*n* mean ± s dev median	*216* 0.19 ± 0.52 0	*101* 0.38 ± 0.75 0
Core period overall	*n* mean ± s dev median	*225* 0.31 ± 0.79 0	*109* 0.58 ± 1.04 0
	p-value for core period overall**	0.005	

**Note that the subject numbers for steroid reduction phase results are not those of the entire intent-to-treat group
*Cochran-Mantel-Haenszel test using midranks, controlling for dose schedule

Mean numbers of hospitalizations in the stable steroid phase were 0 for the omalizumab-treated group and 0.03 in the placebo-treated group; in the steroid reduction phase, 0.01 and 0.03, respectively.

Comments

The quality of life questionnaire data show very little differences in scores between the groups where differences exist. These data do not weigh significantly in the overall assessment of efficacy, however. Numbers of missed subject school days and caregivers work days trended very slightly toward a benefit of omalizumab, but the support is very weak. Data on hospitalizations confirms the relatively well-compensated nature of the subjects in this trial and provides no support for the primary endpoint.

In general, these measures reflected the generally well status of the trial population and were not contributory.

Extension phase evaluations (selected)

During the extension period all subjects were treated with omalizumab, so an assessment of efficacy is not possible due to the lack of a control group. The following is a synopsis of the data presented by Genentech:

- *Asthma exacerbations*

The data were presented on observed exacerbations only; imputation was not performed, and inferential statistics not presented. Table 84 is derived from information corrected by Genentech upon request, as the original BLA contained analyses of exacerbations that had occurred in the followup period in addition to exacerbations that occurred in the extension period.

Table 84. Trial 010: Subjects with asthma exacerbations during the extension phase

	Q2w		Q4w		Overall	
Number of exacerbations	Previous Omalizumab *n=71*	Previous Placebo *n=30*	Previous Omalizumab *n=139*	Previous Placebo *n=69*	Previous Omalizumab *n=210*	Previous Placebo *n=99*
0	56 *79%*	22 *73%*	112 *81%*	58 *84%*	168 *80%*	80 *81%*
1	14 *20%*	7 *23%*	20 *14%*	9 *13%*	34 *16%*	16 *16%*
total ≥1	15 *21%*	8 *27%*	27 *20%*	11 *16%*	42 *20%*	19 *19%*

Sensitivity analysis of extension phase exacerbations

Upon request, Genentech provided data sets with extension phase exacerbations defined using the core period definition of an exacerbation. Table 85 shows an analysis using these data. The overall judgment of a lack of a difference between the groups is maintained. Other analyses, using the core method of imputation or a maximal imputation, yielded similar results (not shown).

Table 85. Trial 010: Subjects with asthma exacerbations during the extension phase

	Q2w		Q4w		Overall	
Number of exacerbations	Previous Omalizumab *n=76*	Previous Placebo *n=35*	Previous Omalizumab *n=149*	Previous Placebo *n=74*	Previous Omalizumab *n=225*	Previous Placebo *n=109*
0	67 *88%*	28 *80%*	129 *87%*	67 *91%*	196 *87%*	95 *87%*
1	8 *11%*	6 *17%*	14 *9%*	6 *8%*	22 *10%*	12 *11%*
total ≥1	9 *12%*	7 *20%*	20 *13%*	7 *9%*	29 *13%*	14 *13%*

*Entire trial population

Comments

Overall there was no difference between the groups in exacerbation rates, suggesting that there was no benefit, nor any dramatic reduction in benefit due to extended treatment, during the extension period. The rates of exacerbations were similar to the omalizumab-treated groups in trials 008 and 009.

- *Mean BDP dose*
  Mean BDP dose did not change appreciably during the extension phase and was very similar between the two treatment groups.
- *FEV_1*
  Mean FEV_1 improved in both groups by about 100 ml, representing an inconsequential change for both groups.
- *FVC and FEF_{25-75}*
  The changes from the start of the extension period to the end of the period paralleled those in FEV_1; that is, similar inconsequential mean improvements were noted in both groups.
- Quality of life questionnaire and missed days of school and caregiver's work: Not reviewed.

Comment

Extension phase evaluations were complicated by the fact that all subjects received omalizumab. Theses evaluations did not show any concerning effects of continued treatment.

Follow-up evaluations

As with trials 008 and 009, the follow-up evaluation occurred after 3 months of no treatment. The proportion of subjects reporting asthma as an adverse event during the follow-up period was 15% in omalizumab-treated subjects (n=206) and 18% in placebo-treated subjects (n=98). These data are inadequate to make a determination of loss or continuation of efficacy during the follow-up period.

Antibody

The antigenicity of omalizumab is discussed in a separate section of this review.

Summary: Efficacy in pediatric trial 010

While trial 010 was not powered for efficacy, it showed a treatment effect in exacerbations that had statistical significance during the steroid reduction phase. The exacerbation data were robust to sensitivity and subgroup analyses. As in trials 008 and 009, a larger proportion of omalizumab-treated subjects was able to discontinue or lower the use of inhaled corticosteroids.

Secondary endpoint data other than exacerbation data tended to reflect the relatively well nature of the trial subjects, showing small differences when differences were observed.

Efficacy during the extension phase was impossible to assess because all subjects were treated with omalizumab; however, there were no efficacy data that would confound the interpretation of efficacy drawn during the controlled phase.

TRIAL 011

Trial 011 was a double-blinded, placebo-controlled trial conducted in adolescents and adults. It was conducted without FDA involvement (outside the IND process). Its usefulness in the overall consideration of omalizumab is primarily in its inclusion of 100 subjects who required treatment with oral corticosteroids. It was designed as a trial to measure steroid reductions, but it also measured asthma exacerbations.

Title

Trial 011 was entitled "A Phase III, 32 week, randomized, double-blind, parallel group, placebo-controlled, multicenter pilot study to assess corticosteroid reduction, efficacy, safety, tolerability, steady state rhuMAb-E25 concentration, and pharmacodynamics of subcutaneous rhuMAb-E25 in adolescents and adults with severe allergic asthma requiring daily treatment with high dose inhaled corticosteroids, with or without oral corticosteroids."

Design

Trial 011 was a double-blind trial of 350 subjects with asthma on corticosteroids randomized 1:1 to omalizumab or to placebo injections for 32 weeks, with a 12 –week follow-up. Separate randomizations were to be done for subjects using either inhaled corticosteroids only (about 250 subjects) or oral corticosteroids with or without inhaled corticosteroids (about 100 subjects). The 32-week period was preceded by a period in which subjects were to be brought to stable doses of fluticasone (inhaled) only or to prednisolone (oral), which could be used in conjunction with fluticasone. Subjects taking long-acting beta-agonists were allowed if the use was established prior to entry; but initiation of long-acting beta-agonist use as well as use of other chronic controller medications were prohibited. The treatment period was divided into a 16-week period during which corticosteroids were to remain stable. Following this was a 12-week period during which corticosteroids were to be reduced, followed by a 4-week period to see if the final dose was a stable one. The treatment period was followed by a period of 10 weeks during which trial treatments were discontinued and restrictions on the use of all other treatments were lifted. Subjects were encouraged to continue on the corticosteroid preparation that they had used during the treatment period, that is, prednisolone or fluticasone or both.

Comments

The stable steroid and steroid reduction phases of this trial mirrored those of the critical efficacy trials submitted in the original marketing application; there was no double-blind extension period as was defined for trials 008 and 009.

Objectives

The primary objective of the trial was to show effects on inhaled corticosteroid use in the group that started on inhaled corticosteroids only. Other objectives were to show effects on oral corticosteroid use, asthma exacerbations, symptoms, and medication use, lung function, trough levels of omalizumab, and pharmacoeconomics.

Trial treatments

Placebo or omalizumab were to be administered by subcutaneous injection by trial personnel. Subjects randomized to omalizumab received omalizumab at the proposed dose according to the same dosing table that was used in the critical efficacy trials 008 and 009 (Table 14).

Concomitant medications

Subjects were to take inhaled fluticasone or oral prednisolone as commercially available, according to their group. Inhaled β agonists, short- and medium-acting antihistamines, nasal corticosteroids (excluding preparations containing dexamethasone), and short-term mild or moderately potent topical steroids were allowed. Initiation of allergen desensitization immunotherapy was prohibited, but subjects who were already treated with it for ≥3 months at stable doses were required to continue.

Numerous medications were not allowed during the trial including oral, parenteral, regular nebulized, or any inhaled β-2 agonists other than the prescribed rescue (as required) medication unless given during treatment of an exacerbation; cromolyn sodium or nedocromil sodium, parenteral corticosteroids (except for treatment of asthma exacerbations), leukotriene receptor inhibitors and 5-lipoxygenase enzyme inhibitors, oral or inhaled anticholinergic therapy, long-acting antihistamines, theophyllines, β-adrenergic antagonist medications, or any investigational, experimental, or nonapproved drugs. Long-acting inhaled ß-2 agonists and theophyllines were not allowed to be initiated during the trial.

Comments

As in the critical efficacy trials, many possible concomitant medications for asthma were prohibited, effectively limiting the primary analytical population to subjects who could be managed with a modest amount of medication. While the inclusion of subjects who required oral corticosteroid partially mitigated this fact, these were not the subjects of the trial's primary objective.

Blinding

Omalizumab was shipped to sites open-label; placebo was shipped with the labels "A" and "B." They were prepared for administration by personnel designated at trial sites according to a randomization list provided by Novartis; these persons were not to reveal the identity of medications to anyone responsible for conducting, monitoring, or analyzing the trial. Personnel preparing and administering trial medication were not to be involved in subject evaluations.

Subject qualifications

Subjects were screened, then entered a run-in period. Subjects were randomized after meeting screening and certain run-in criteria.

Inclusion criteria

- Males or females, 12-75 years old
- Receipt of inhaled corticosteroids for ≥1 year
- ≥1000 µg/day fluticasone at screening and 1000-2000 µg/d at randomization with or without oral corticosteroid use at screening and prednisolone up to 20 mg/d at randomization
- Mean total daily symptom score <4 over 7 days prior to randomization

  Note: the total is scored in the same way as in the critical efficacy trials, that is, a total of nocturnal asthma score (0-4 scale), morning asthma symptoms (yes, no), daytime asthma symptom score (0-4 scale)
- Serum IgE >30 IU/ml and <700 IU/ml
- Positive skin prick test to ≥1 allergens (house-dust mite or animal dander (cat, dog) or if the skin test is "borderline," a positive RAST test (>0.7 PRU/ml) to these allergens
- ≥12% improvement in FEV1 over baseline with inhalation of β-agonist, documented within the past year or at screening or run-in
- Continued exposure to allergen to which positive tests are demonstrated

- Daily fluticasone dose no greater than 250 µg more than the dose established 4 weeks prior to randomization
- Daily prednisolone dose no greater than 2.5 mg more than the dose established 4 weeks prior to randomization
- No additions to asthma treatment during the 4 weeks prior to randomization

- "Acceptable medical history and physical examination and acceptable laboratory test results"

Exclusion criteria (selected)

- History of severe anaphylactoid or anaphylactic reaction
- Asthma due to ASA or NSAIDs unless avoidance of such drugs can be expected
- Smoking within 2 years of visit 1, or history of smoking >10 pack years
- Active lung disease other than allergic asthma
- Elevated serum IgE for reasons other than atopia
- Desensitization treatment with less than 3 months of stable maintenance dosing prior to visit 1
- Use of excluded medications (see concomitant medication section) within specified times of visits 1 and 3
- Clinically significant disease or history of such a disease
- History of near-fatal asthma attack (respiratory arrest or $PaCO_2$ ≥50 mmHg within the prior 3 years)

Comments

The principal difference in enrollment criteria between this population and that in the critical efficacy trials is permitting the use of oral corticosteroids in some subjects. However, as in the critical efficacy trials, the trial population's asthma severity was limited. Subject qualifications that limited asthma severity included: exclusion of the use of methotrexate and other medications for refractory asthma; limitations on the concurrent use of different anti-asthma medications; a ceiling on the oral corticosteroid use (no more than 20 mg/d of prednisolone), and the exclusion for near-fatal asthma attack in the last 3 years.

Randomization

A separate randomization was performed for subjects requiring oral corticosteroids and those not requiring oral corticosteroids.

Procedures and evaluations

Corticosteroid management

Subjects were screened, then entered into a 6- to10-week run-in phase. During this phase, potential subjects were switched from their inhaled or oral corticosteroids to fluticasone or prednisolone, respectively. These corticosteroids were then reduced in protocol-defined increments every 2 weeks; in subjects taking both types of corticosteroids, the prednisolone was eliminated before a reduction in fluticasone was attempted. Corticosteroid reduction for potential subjects proceeded unless the following occurred:

- a >50% increase in 24 hour rescue medication use on at least 2 of any 3 consecutive days compared to mean use during the 7 days prior (must also exceed the equivalent of 8 puffs salbutamol MDI
- mean daily total asthma symptom score >4 over 7 days prior to the run-in
- fall in the morning PEF of > 20% on at least 2 of any 3 consecutive days as compared to the mean morning PEF of the 7 days prior
- worsening of the disease between visits requiring an unscheduled practitioner/hospital visit

- at least 2 of any 3 consecutive nights with awakenings due to asthma symptoms requiring rescue medication
- an asthma exacerbation

If one of these occurred, the dose of corticosteroid was then increased until no criterion was met.

Randomization occurred if the dose of corticosteroids was maintained stable for 4 weeks and the dose of fluticasone was 1000-2000 μg/d, or the prednisolone dose was ≤20 mg/d.

Attempts at corticosteroid reduction were made during the first 12 weeks of the corticosteroid reduction phase, with 4 additional weeks to assess the durability of the dose attained. Protocol-defined graded decrements in inhaled or oral dose were attempted every 2 weeks. For subjects on prednisolone, fluticasone was not reduced during this phase. Reductions were attempted until the dose was 0 or the subject became symptomatic as defined above. Discontinuation of fluticasone was allowed only if the subject required on average, over the preceding week, <4 puffs/d of rescue inhaled β agonist. If a subject were to become symptomatic, steroids were increased until the symptoms abated. Further attempts at dose reduction were made unless a previous attempt had resulted in a hospitalization or there was more than 1 failed attempt.

During the follow-up phase, subjects were encouraged to continue on prednisolone or fluticasone, or both, as appropriate.

Recording of pulmonary function at home and management of exacerbations

Subjects were issued peak flow meters and instructed and monitored in their use. As in the critical efficacy trials, instructions were provided to the subjects to notify their investigator for evaluation for any of the following:

- worsening of asthma at any time requiring an urgent (unscheduled) visit for medical care
- PEFR <50% of patient's personal best
- a decrease in morning PEFR of ≥20% on ≥2 of 3 successive days, compared to the mean morning PEFR of the 7 days prior to the run-in
- a ≥50% increase in 24-hour rescue medication use on ≥2 of 3 successive days, compared to the7 days prior to the run-in (must exceed equivalent of 8 puffs of salbutamol)
- ≥2 of 3 successive nights with awakenings due to asthma symptoms requiring rescue medication

Asthma exacerbations were to be treated as deemed appropriate. If steroids were to be used, the recommended regimen was prednisolone, 40-60 mg/d, for 3-10 days.

Schedule of important procedures

1-week screening (visit 1)

The screening period lasted 1 week.

10-week run-in (5 every-2-week visits, 2.1-2.5)

- Physical; collect and review diaries, adverse events, and concomitant medications
- FEV_1, FVC, and FEF_{25-75}
- Review medication use

16-week double-blind stabilization period (8 every-2-week visits: 3-6.1)

visits 3, 4, 5, and 6

- Physical; collect and review diaries, adverse events, and concomitant medications; issue diary cards; CBC/diff, serum chemistries
- FEV_1, FVC, and FEF_{25-75}
- Total IgE

visits 3.1, 4.1, 5.1, and 6.1

- FEV_1, FVC, and FEF_{25-75}

16-week double-blind steroid reduction phase (9 every-2-week visits: 7-15)

- Physical; collect and review diaries, adverse events, and concomitant medications; CBC/diff, serum chemistries; quality of life questionnaires at visits 7, 11, and 15
- FEV_1, FVC, and FEF_{25-75}
- Pharmacokinetics/pharmacodynamics at visits 7 and 13/14
- Total IgE
- Review steroid dosage and attempt reduction

10-week follow-up period (4 every-2-week visits: 16-19)

- Review adverse events and concomitant medications; CBC/diff, serum chemistries
- Total IgE
- FEV_1, FVC, and FEF_{25-75} at visit 19

Analytical plan

Efficacy variables

1° endpoint

The primary variable was the percent reduction in inhaled corticosteroid dose at the end of the steroid reduction phase compared to baseline (visit 15 compared to visit 3). The population for this determination was the group taking inhaled corticosteroids, but not oral corticosteroids, at randomization.

The analysis compensated for instability of dosing in the last 4 weeks, which would make a final dose uncertain. In order to use all subject data, the analysis used the maximal dose among the final 3 visits, unless there had been an asthma exacerbation within the time period of the last 3 visits. In this case, the final dose was set as the maximal dose in the last 5 visits. If dose data were not available for all of the last 3 visits, the final dose was equal to the dose at the beginning of steroid reduction. These rules were not established in the protocol but were established prior to unblinding the data.

The protocol specified that the analytical population excluded those who did not complete the treatment stabilization and steroid withdrawal phases or who committed a "major" protocol violation (major protocol violations were not listed in the protocol; they were determined before data base lock and unblinding.) However, the report of the trial states that the primary analytical population was all randomized subjects.

The statistical test was to be the van Elteren test stratified by treatment schedule. Patients who did not enter the steroid-sparing phase were to be included in the analysis with 0% inhaled steroid dose reduction. Patients who discontinued prematurely during the steroid reduction phase were to be included in the analysis using the final dose of inhaled steroid recorded.

2° endpoints

The protocol specified 28 secondary endpoints, divided into endpoints determined during the stable steroid and steroid reduction phases separately. The following list shows how they were ordered in the protocol:

During the stable steroid phase

1. Mean daily dose of inhaled steroid (patients on inhaled steroid, but not on oral steroid, at baseline)
2. Mean daily dose of oral steroid (patients on oral steroid at baseline)
3. Number of patients experiencing at least one asthma exacerbation
4. Number of exacerbation episodes per patient
5. Number of puffs of rescue medication taken during the day and the night

6-11: Peak expiratory flow, FEV_1, FVC, and FEF_{25-75}

During the steroid reduction phase:

Items 12-16 are for subjects on inhaled steroids only at baseline

12. Absolute reduction in inhaled steroid dose at end of treatment phase (Visit 15) compared to baseline (Visit 3)
13. Mean daily dose of inhaled steroid
14. Proportion of patients with a successful reduction of inhaled corticosteroids (>=50% dose reduced) relative to baseline
15. Proportion of patients with a complete withdrawal of inhaled corticosteroids (100% removal) relative to baseline
16. Time to cessation of inhaled steroid dose reduction due to loss of asthma control

Items 17-22 were for subjects on oral corticosteroids at baseline

17. Percentage reduction in oral steroid dose at end of treatment phase compared to baseline (Visit 3)
18. Absolute reduction in oral steroid dose at end of treatment phase compared to baseline (Visit 3)
19. Mean daily dose of oral steroid
20. Proportion of patients with a successful reduction of oral steroids (>=50% dose reduced) relative to baseline
21. Proportion of patients with a complete withdrawal of oral steroids (100% removal) relative to baseline
22. Time to cessation of oral steroid dose reduction due to loss of asthma
23. Percentage reduction in oral or inhaled corticosteroids
24. Number of patients experiencing at least one asthma exacerbation
25. Number of exacerbation episodes per patient
26. Number of puffs of rescue medication taken during the day and the night
27. Subject and investigator global evaluation

28-33. Peak expiratory flow, FEV_1, FVC, and FEF_{25-75}

Comment

The protocol was designed to capture similar endpoints to those measured in the critical efficacy trials.

Analysis of exacerbations

Asthma exacerbations were defined as a worsening of asthma necessitating initiation of systemic corticosteroids. The initiation of systemic corticosteroids marked the start of an exacerbation and the cessation of corticosteroids the end.

The number of exacerbations for subjects discontinuing was imputed as in the critical efficacy trials, that is, rounded to the nearest integer: Number observed + (days between discontinuation and end of period)/14.

If a subject were to discontinue during the stable steroid phase, the number of exacerbations for the subject during the steroid reduction phase was the maximum calculated + 1.

The statistical test for the between-treatment difference in the number of asthma exacerbation episodes was to be performed using the Cochran-Mantel-Haenszel test. This was to test whether there was a mean score location shift. The analysis was to be stratified by treatment schedule when performing the analysis separately for the different baseline steroid groups, but stratified by baseline steroid use when performing the analysis on all patients. The weights given to the counts were to use the standardized midrank.

Comments

The protocol definition of an asthma exacerbation in trial 011 was more stringent than the one used in trials 008 and 009. In trial 011, systemic corticosteroids were required to meet the protocol criterion1. In trials 008 and 009, a doubling of inhaled corticosteroids could suffice to determine protocol acceptability.

The statistical analysis of exacerbations was the same as that of the critical efficacy trials. The method imputed a large number of exacerbations to discontinuers, as in the critical efficacy trials. This method has the potential to bias the results markedly. Its impact on the results will be shown in the results section.

Interim analysis

No interim analysis was planned or performed.

Protocol modifications

One protocol amendment was made several months after the recruitment of the first subject (see dates of the trial). An amendment dated December 9, 1998 allowed subjects into the trial if they used nebulized β agonists, removed a maximal time for subjects to have been on oral corticosteroids at inclusion, allowed FEV_1 reversibility to be shown at run-in (not only at screening), and allowed potential subjects with ASA- or NSAID-related asthma into the trial if they could be relied upon to avoid such drugs. Other minor changes to the protocol were made in the amendment. None of the changes would have been expected to have an impact on the interpretation of the results of the trial.

Results: Conduct of the trial

Dates of the trial

The first subject was recruited into the trial on August 14, 1998, and the last subject completed the trial on May 22, 2000.

Trial site conduct

During the trial one site (enrolling 3 subjects in each treatment group in the primary analytical group and 5 total (3 omalizumab and 2 placebo) in the oral corticosteroids group) was closed due to concerns over trial conduct at the site. Details over the conduct issue are not provided.

Comments

The trial sponsor was aware of the trial conduct issues at the site and reports no other trials with important conduct issues.

Screening failures

Table 86 shows the number screened and the reasons for failure to be enrolled. A total of 21% of potential enrollees were out of range of the IgE criteria. This is a slightly higher proportion than were screened out of trials 008 and 009 (about 15%). The majority of screen failures due to IgE were excluded due to serum IgE that was too high.

Table 86. Trial 011: Screening failures

Total number of patients screened	**706**
Number of patients randomized into the study	**341 (48%)**
Number of patients excluded from the study	**365 (52%)**
Reason for exclusion	
IgE out of range <30	43 (6%)
IgE out of range >700	103 (15%)
Fluticasone > 2000 μg/day at visit 3	2 (0.3%)
Fluticasone < 1000 μg/day at visit 3	50 (7%)
Reversibility <12%	12 (2%)
Combination of IgE and body weight for dosing too high	6 (1%)
Skin test negative	37 (5%)
Medical history, lab results, ECG, chest X-ray, smoking history, pregnancy, active lung disease	56 (8%)
Withdrew consent, non-compliance, medications, wants to get pregnant, other	56 (8%)

Comment

As for the critical efficacy trials, a significant proportion was screened out for reasons of IgE unacceptability.

Enrollment by site

None of the 34 sites enrolled a predominating number of subjects (Table 87).

Table 87. Trial 011: Enrollment by site

Number of subjects	Number of sites
1-5	13
7-10	6
11-15	10
16,20	2
24, 26, 27	1,1,1

Demographics and baseline characteristics

Table 88 shows that baseline demographics were well balanced between treatment arms. As in the critical efficacy trials 008 and 009, the majority of subjects were female. The great majority of subjects were Caucasian. A small proportion of subjects were in the geriatric age range.

Table 88. Trial 011: Demographics (subjects, % unless otherwise indicated)

	Omalizumab n=176	Placebo n=165
Sex		
Male	63 (36)	66(40)
Female	113 (64)	99 (60)
Race		
Caucasian	146 (83)	136 (82)
Black	0	3 (2)
Oriental	2 (1)	1 (1)
Other	28 (16)	25 (15)
Age (yr.)		
Mean range	42.7 12-75	42.5 12-74
12-17	12 (7)	9 (6)
18-64	150 (85)	146 (89)
≥65	14 (8)	10 (6)
Duration of asthma (yr.) Mean range	 22.3 2 – 70	 22.3 1 – 64
Never smoked	136 (77)	123 (75)

Table 89 shows selected baseline subject characteristics, which were generally well balanced across groups. However, the following are notable: 1) Visits for medical care were slightly higher in proportion in the omalizumab-treated group in the inhaled corticosteroid users; and 2) There were greater proportions of subjects with overnight hospital admissions in the previous year in the oral corticosteroid group, and a trend toward more urgent emergency room visits and missed work/school days. It should be noted that the numbers of subjects in the oral corticosteroid group are small, making quantitative comparisons between this group and the group on inhaled corticosteroids uncertain.

Table 89. Trial 011: Baseline subject characteristics*

	Inhaled corticosteroid only		Oral corticosteroid	
	Omalizumab *n=126*	**Placebo *n=120***	**Omalizumab *n=50***	**Placebo *n=45***
Fluticasone dose (μg/day)	1375 (750 – 2000)	1363 (1000–2000)	1490 (750 – 2500)	1411 (500–2000)
Prednisolone dose (mg/d)	-	-	10 (2.5 – 25)	10.6 (1.3–30)
Serum total IgE (IU/ml)	267 (31 – 1055)	266 (19 – 815)	205 (26 – 610)	234 (23–701)
% predicted FEV_1 visit 1	63 (17 – 119)	66 (8 – 123)	60 (16 – 98)	57 (32–98)
FEV_1 reversibility (%) visit 1	19 (-99 – 93)	21 (-90–110)	20 (-4.5 – 65)	23 (-29–115)
Qualifying FEV_1 reversibility (%)	25 (-99 – 93)	27 (11–111)	24 (12 – 65)	27 (10–115)
Overnight hospital admission, past year n (%)	16 (13%)	8 (6.7%)	11 (23%)	10 (23%)
Emergency Room visits, past year	0.7 (0-8)	0.6 (0-10)	1.0 (0-10)	1.3 (0-20)
Doctor's office visits, past year	2.1 (0-20)	1.7 (0-10)	2.2 (0-10)	1.7 (0-12)
Missed work/school days, past year	6.3 (0-56)	6.4 (0-88)	7.8 (0-90)	9.7 (0-229)

*means and ranges unless otherwise specified

Allergic history was prevalent. Most subjects had history of sensitivity to dust mites, smaller proportions, but still a clear majority, had a history of sensitivity to animals and aeroallergens.

Comments

The proportion of subjects with an overnight hospitalization in the last year was greater overall than in trials 008 and 009, where the proportions were around 3 and 7%, respectively. More omalizumab- than placebo-treated subjects in the inhaled group were hospitalized for asthma in the previous year, suggesting that this group had at least a subset of subjects who experienced more severe exacerbations. The group on oral corticosteroid had predictably a higher incidence of hospitalizations than the group on inhaled corticosteroids.

Subject disposition

Table 90 and shows the disposition of subjects up to the end of the steroid reduction phase. Although there were overall a similar proportion of subjects who discontinued during the combined stable steroid and steroid stabilization periods, there were clearly proportionately more discontinuations in the omalizumab group during the stable steroid period.

Table 90. Trial 011: Subject disposition (n, (%))

	Omalizumab	Placebo
Randomized	176 (100)	165 (100)
Discontinued before followup period	16 (9)	14 (9)
Discontinued during stabilization period	11	5
Adverse event	1	1
Abnormal lab value	1	1
Insufficient efficacy	0	1
Protocol violation	2	0
Withdrew consent	6	1
Lost to follow-up	0	1
Administrative	1	0
Discontinued during steroid reduction phase	5	9
Adverse event	0	1
Abnormal lab value	0	0
Insufficient efficacy	0	1
Protocol violation	1	1
Withdrew consent	2	2
Lost to follow-up	0	1
Administrative	2	3
Discontinued during follow-up period	10	9
Adverse event	0	1
Abnormal lab value	0	1
Insufficient efficacy	0	1
Protocol violation	1	0
Withdrew consent	7	2
Lost to follow-up	0	1
Administrative	2	3

Reasons for withdrawal of consent (provided only for the period before the follow-up period) showed no distinct asthma-related pattern. Based on relatively small numbers of events for each type of event, the relative incidences of reasons for discontinuation in the oral and inhaled subgroups were otherwise generally similar.

Among the subjects discontinued due to administrative reasons were 3 subjects at site 161, which was closed during the trial due to concerns over trial conduct.

As Table 91 shows, omalizumab subjects tended to discontinue earlier than placebo subjects.

Table 91. Trial 11: Visit at discontinuation, to end of steroid reduction phase

Visit at discontinuation	3	4	5	6	7	8	11	12	13	14	15
Placebo	0	2	1	2	2	0	3	2	0	2	0
Omalizumab	5	1	4	1	1	1	1	0	1	0	1

Comment

The pattern of discontinuations combined with the imputation technique would falsely inflate the number of exacerbations in the omalizumab group compared to placebo. See the section of the review on secondary endpoints for a review of the effect that discontinuations had on the analysis of exacerbations.

Protocol violations

Table 92 shows important protocol violations to the end of the steroid reduction phase. Protocol violations were not assessed during the follow-up period.

Table 92. Trial 011: Subjects with selected protocol violations to the end of the steroid reduction phase (n, %)

	Inhaled		Oral		Overall	
	Omlzmb (N=126)	Placebo (N=120)	Omlzmb (N=50)	Placebo (N=45)	Omlzmb (N=176)	Placebo (N=165)
Steroid adjustment in run-in phase	35(28)	22(18)	25(50)	20(44)	60(34)	42(25)
Run-in steroid adjustment not per protocol	30(24)	20(17)	20(40)	17(38)	50(28)	37(22)
Change in steroid dose in last 4 weeks of run-in	7(6)	1(1)	4(8)	3(7)	11(6)	4 2.4)
Fluticasone dose at visit 3 <1000 or >2000 µg	2(2)	0	2(4)	1(2)	4(2)	1 0.6)
Dose of fluticasone at visit 2.1 <750 µg	0	1(1)	1(2)	2(4)	1(0.5)	3(2)
Dose of prednisolone at visit 3 >20 mg/d	0	0	1(2)	1(2)	1(0.5)	1(0.6)
Steroid adjustment in steroid-reduction phase	15(12)	9(8)	20(40)	21(47)	35(20)	30(18)
Steroid dose reduction after visit 13	14(11.1)	8(7)	4(8)	5(11)	18(10)	13(7.8)
Reduction in inhaled dose for oral patients	0	0	13(26)	13(29)	13(7.3)	13(7.8)
Steroid reduction not per protocol	2(1.5)	1(0.8)	10(20)	8(18)	12(6.8)	9(5)
IgE/body weight outside dosing table range	16(13)	17(14)	3(6)	6(13)	19(11)	23(14)
Dosing ≥ 0.007 mg/kg/IU/ml Q2w	9(7)	12(10)	2(4)	3(7)	11(6)	15(9)
IgE > 700 IU/ml and dosing ≥0.007mg/kg/IU/ml twice weekly	7(6)	3(3)	0	1(2)	7(4)	4(2)
IgE <30 IU/ml	0	2 (2)	1 (2)	2 (4)	1 (1)	4 (2)
Baseline mean asthma symptom score ≥4	7(6)	6(5)	9(18)	6(13)	16(9)	12(7.2)
Baseline mean asthma symptom score ≥4 - 6	5(4)	5(4)	8(16)	5(11)	13(7)	10(6.0)

Overall, the most common important violation category was steroid dose adjustment in the run-in phase. The submission states that because of this "a true minimum corticosteroid dose could not be confirmed." Steroid adjustment violations occurred to a moderate degree during the steroid reduction phase too. More of these violations occurred in the oral corticosteroid subjects than in the inhaled corticosteroid subjects.

Comment

As is mentioned below, there was no notable effect of steroid adjustment violators on the estimation of the treatment effect on steroid reduction.

Exposure to product

Table 93 shows that about 80% of all subjects received at least the 32 protocol-defined weeks of treatment, and the majority of the remaining subjects received between 28-32 weeks of treatment. The exposure durations were well balanced.

Table 93. Trial 011: Weeks of exposure to trial agent

Weeks	Inhaled		Oral		Overall	
	Omlzmb *(n=126)*	Placebo *(n=120)*	Omlzmb *(n=50)*	Placebo *(n=45)*	Omlzmb *(n=176)*	Placebo *(n=165)*
<28	11 (9%)	10 (8%)	3 (6%)	2 (4%)	14 (8%)	12 (7%)
28 - <32	18 (14%)	11 (9%)	8 (16%)	11 (24%)	26 (15%)	22 (13%)
≥32	97 (77%)	99 (83%)	39 (78%)	32 (72%)	136 (77%)	131 (79%)

Results: Efficacy

Primary endpoint

The primary endpoint was an analysis of the percentage reduction in fluticasone in the group who used inhaled corticosteroid only (Table 94). Baseline use of fluticasone was comparable between the treatment groups (see baseline characteristics).

Table 94. Trial 011: Percentage reduction in inhaled corticosteroid dose (group on inhaled corticosteroids only, intent-to-treat)

	Q2 week		Q4 week		Overall		
	Omlzmb *n=63*	Placebo *n=64*	Omlzmb *n=63*	Placebo *n=56*	Omlzmb *n=126*	Placebo *n=120*	
median	50.0	46.4	60.0	50.0	60.0	50.0	p-value 0.003 *
range	-33.3 – 100	-60 – 100	-75 – 100	-100 – 100	-75 – 100	-100 – 100	

* Generalized CMH (van Elteren) test using standardized midranks and controlling for dosing schedule

Table 95 shows corticosteroid reductions expressed as proportions of subjects having different amounts of reductions in inhaled corticosteroid use from baseline. Generally, larger proportions of subjects treated with omalizumab reduced fluticasone use in the larger percent reduction categories. A small number of subjects increased their steroid dose, reflected by a reduction of less than 0%.

Table 95. Trial 011: Subjects (%) by reduction in inhaled corticosteroid use from baseline (group on inhaled corticosteroids only)

	Q2w		Q4w		Overall	
Percent reduction in inhaled steroid dose	**Omlzmb *n=63***	**Placebo *n=64***	**Omlzmb *n=63***	**Placebo *n=56***	**Omlzmb *n=126***	**Placebo *n=120***
100%	15 (24%)	7 (11%)	12 (19%)	11 (20%)	27 (21%)	18 (15%)
75% to <100%	11 (18%)	7 (11%)	14 (22%)	6 (11%)	25 (20%)	13 (11%)
50% to <75%	19 (30%)	18 (28%)	22 (35%)	12 (21%)	41 (33%)	30 (25%)
25% to <50%	4 (6%)	15 (23%)	7 (11%)	9 (16%)	11 (9%)	24 (20%)
>0% to <25%	3 (5%)	2 (3%)	1 (2%)	3 (5%)	4 (3%)	5 (4%)
0% (no change)	9 (14%)	13 (20)	5 (8)	14 (25)	14 (11)	27 (23)
<0%	2 (3%)	2 (3%)	2 (3%)	1 (2%)	4 (3%)	3 (3%)

Comments

A remarkable finding in the examination of inhaled corticosteroid reductions is the large number of placebo subjects who reduced steroids. Half of the subjects reduced the corticosteroid dose by at least 50% of their dose. This suggests that during the stable steroid phase, the amount of inhaled corticosteroid use was somewhat in excess of the minimum required by these subjects, and may have reduced the symptomatology during that phase. It is possible that the considerable number of protocol-inappropriate steroid reductions during run-in reduced the achievement of a truly minimal dose. On the other hand the percents reduction in inhaled corticosteroid use were in much smaller than those seen in trials 008 and 009, where the percents reducing their inhaled corticosteroid use by 100% were from 40-44% (omalizumab) to 19% (placebo).

Sensitivity analysis of primary endpoint

Analyses of steroid reductions in a population of subjects excluding subjects with protocol violations of steroid adjustment during any phase of the trial were consistent with the ITT analysis.

Secondary endpoints

- *Secondary endpoint: reduction in steroid use*

Oral corticosteroid users

Table 96 shows that there was a weak trend for reductions in oral corticosteroids to be less in the omalizumab group than in the placebo group. This suggests that omalizumab did not confer any advantage to asthma management in oral corticosteroid users.

Table 96. Trial 011: Percentage reduction in oral corticosteroid dose (group on oral corticosteroids only)

	Q2 week		Q4 week		Overall		
	Omlzmb *n=21*	**Placebo *n=20***	**Omlzmb *n=29***	**Placebo *n=25***	**Omlzmb *n=50***	**Placebo *n=45***	
median	100	100	50	75	69	75	p-value 0.675*
range	-357 – 100	0 – 100	-60 – 100	-20 – 100	-357 – 100	-20 – 100	

* Generalized CMH (van Elteren) test using standardized midranks and controlling for dosing schedule

Table 97 shows that a substantial number of subjects from the placebo as well as the omalizumab group discontinued entirely or nearly entirely from oral corticosteroids, suggesting that

in general subjects were overtreated with oral corticosteroids during the steroid stabilization period The distribution of percents reduction in oral corticosteroid was similar between the two treatment groups, consistent with the summary results. This illustrates that there was no benefit of the administration of omalizumab to oral corticosteroid users in reduction of oral corticosteroid use.

Table 97. Subjects (%) by reduction in oral corticosteroid use from baseline

	Q2w		Q4w		Overall	
Percent reduction in oral steroid dose	Omlzmb n=21	Placebo n=20	Omlzmb n=29	Placebo n=25	Omlzmb n=50	Placebo n=45
100%	12 (57%)	11 (55%)	9 (31%)	8 (32%)	21 (42%)	19 (42%)
75% to <100%	2 (10%)	2 (10%)	2 (7%)	5 (20%)	4 (8%)	7 (16%)
50% to <75%	1 (5%)	2 (10%)	6 (21%)	1 (4%)	7 (14%)	3 (7%)
25% to <50%	1 (5%)	0	4 (14%)	4 (16%)	5 (10%)	4 (9%)
>0% to <25%	0	0	0	0	0	0
0% (no change)	3 (14%)	5 (25%)	5 (17%)	6 (24%)	8 (16%)	11 (24%)
<0%	2 (10%)	0	3 (10%)	1 (4%)	5 (10%)	1 (2%)

- *Secondary endpoint: asthma exacerbations*

Inhaled corticosteroid users

Asthma exacerbations were the primary endpoint events in the critical efficacy trials. As stated in the discussion of analysis of asthma exacerbations, the protocol criterion for corticosteroid treatment of an exacerbation in trial 011 was higher than that used in the critical efficacy trials (systemic use, as opposed to an allowed doubling of inhaled corticosteroids in trials 008 and 009).

Among the placebo subjects most exacerbations were of unknown cause. Most asthma exacerbations in the omalizumab group were the result of either a "chest infection" or a "viral infection/upper respiratory tract infection."

Table 98 shows Genentech's analysis of exacerbations, in the inhaled corticosteroid-using group only. Using the protocol-defined technique of imputation, mean exacerbations in the omalizumab group exceeded those in the placebo group during both the stable steroid and steroid reduction phases. The imputation technique, as for the trials 008 and 009, markedly increased calculated exacerbation rates for early discontinuers. In trial 011, there were more early discontinuers in the omalizumab group.

Table 98. Trial 11: Asthma exacerbations, inhaled corticosteroid only group (protocol-defined imputation)

	Omalizumab *n=126*	**Placebo *n=120***
Stabilization phase		
Number (%)		
0	106 (84)	102 (85)
1	7	9
2	7	3
3	1	1
≥4	5	5
≥1	20 (16)	18 (15)
Median [range]	0 [0 – 8]	0 [0 – 7]
Mean	0.45	0.38
p-value*	0.85	
Reduction phase		
Number (%)		
0	98 (78)	88 (73)
1	13	16
2	3	4
3	1	3
≥4	11	9
≥1	28 (22)	32 (27)
Median [range]	0 [0 – 10]	0 [0 – 10]
Mean	0.98	0.92
p-value*	0.50	

*Generalized Cochran-Mantel-Haenszel (van Elteren) test using standardized midranks and controlling for dosing schedule

Sensitivity analyses

Alternative imputation techniques applied to the data are shown in Table 99. In the addition of 1 exacerbation, 1 additional exacerbation was imputed in the stable steroid phase to subjects who discontinued early in the stable steroid phase, and 1 exacerbation to these subjects in the steroid reduction phase. These techniques impute exacerbations in a manner more reflective of the overall population behavior, and thus place less bias against early discontinuers.

Mean exacerbation rates were better for omalizumab in both phases for both methods (but there was no difference in numbers of subjects with at least 1 exacerbation in the stable steroid phase using the imputation of 1 additional exacerbation). The nominal standard of statistical significance ($p<0.05$) was not reached in any analysis for either period.

Table 99. Trial 11: Sensitivity analyses of asthma exacerbations, inhaled corticosteroid only group

	No imputation		Impute 1 additional	
Stabilization phase				
	Omalizumab *n=126*	**Placebo *n=120***	**Omalizumab *n=126***	**Placebo *n=120***
Number (%)				
0	113 (90)	105 (88)	106 (84)	102 (85)
1	7	10	14	12
2	6	2	6	3
3	0	1	0	1
≥4	0	2	0	2
≥1	13 (10)	15 (13)	20 (16)	18 (15)
Median [range]	0 [0 – 2]	0 [0 – 6]	0 [0 – 2]	0 [0 – 6]
Mean	0.15	0.23	0.21	0.26
p-value**	0.57		0.91	
Reduction phase				
	Omalizumab *n=117**	**Placebo *n=115****	**Omalizumab *n=126***	**Placebo *n=120***
Number (%)				
0	100 (85)	90 (78)	98 (78)	88 (73)
1	13	19	24	23
2	3	4	3	7
3	1	1	1	1
≥4	0	1	0	1
≥1	17 (15)	25 (22)	28 (22)	32 (27)
Median [range]	0 [0 – 3]	0 [0 – 9]	0 [0 – 3]	0 [0 – 9]
Mean	0.19	0.34	0.26	0.41
p-value**	0.15		0.35	

*not the intent-to-treat population

** Generalized Cochran-Mantel-Haenszel (van Elteren) test using standardized midranks and controlling for dosing schedule

Comments

Table 100 shows a comparison of the effect sizes in trials 008-010 and that in trial 011 (inhaled corticosteroid group) expressed as proportions of subjects with at least 1 exacerbation. Table 100 shows that during the stable steroid phase the effect size was smaller in trial 011, but during the steroid reduction phase it was similar. These results suggest that the lack of statistical significance in trial 011 is bifactorial. During the stabilization phase, the effect seen in trials 008-010 was not observed to as great an extent; during the steroid reduction phase, the smaller trial population contributed to the lack of statistical significance.

Table 100. Comparison of effect sizes in trials 008-011 (subjects (%) with at least 1 exacerbation, observed, ITT population)

Trial	phase	Omalizumab	Placebo
	n	*268*	*257*
008	Stable steroid	30 (11%)	47 (18%)
	Steroid reduction	39 (15%)	51 (20%)
	n	*274*	*272*
009	Stable steroid	27 (10%)	63 (23%)
	Steroid reduction	26 (9%)	44 (16%)
	n	*225*	*109*
010	Stable steroid	28 (12%)	20 (18%)
	Steroid reduction	27 (12%)	31 (28%)
		Inhaled corticosteroid only	
011	*n*	*126*	*120*
	Stable steroid	13 (10%)	15 (13%)
	Steroid reduction	17 (13%)	25 (21%)

Subgroup analyses of exacerbations in inhaled corticosteroid users

Subgroup analyses of proportions of subjects with at least 1 exacerbation, using observed exacerbation numbers, in various subgroups of the inhaled corticosteroid users (Appendix Table 165 and Table 166) show:

- Race: "Whites" predominated in the trial and contributed mostly to the effect; there were too few subjects in the category "Black" and "Oriental" for differences based on these categories to be reliably discerned. There were too few exacerbations in the "Other" race category for a trend to be observed.
- Baseline predicted percent FEV_1, dichotomized at 80%: The treatment trends were not sensitive to this dichotomization.
- Sex: Females saw a trend toward a treatment effect during the stable steroid phase, while males did not; both sexes saw a trend toward a treatment effect in the steroid reduction phase.
- Age: There were too few subjects at the extremes of age (<17 years old or ≥65 years old) for differences based on these categories to be reliably discerned.
- Number of allergens (1-4): Numbers of subjects with only 1 allergen sensitivity were too small for useful analysis; in the groups with 2-4 allergen sensitivities, the largest treatment trend was seen in the group with 2 allergen sensitivities.
- Baseline IgE, in quartiles: There was no difference in effect with increasing baseline IgE.
- Body mass, in quartiles: In the highest body mass category only (≥85 kg) omalizumab-treated subjects did worse than those on placebo.
- Baseline inhaled dose corticosteroid, in tertiles: There was no trend toward a difference in effect.

Comments

The overall group of inhaled corticosteroid users was small, and the overall effect size was small, making it problematic to draw firm conclusions from these data. Small differences in effects could have a large impact on the results.

Oral corticosteroid users

Table 101 shows that the protocol-defined analysis resulted in more exacerbations among oral corticosteroid users during both phases.

Table 101. Trial 11: Asthma exacerbations, oral corticosteroid group (protocol-defined imputation)

	Omalizumab ***n=50***	**Placebo** ***n=45***
Stabilization phase		
Number		
0	34 (68)	35 (78)
1	9	6
2	2	2
3	2	2
≥4	3	0
≥1	16 (32)	10 (22)
Median [range]	0 [0 – 8]	0 [0 –3]
Mean	0.78	0.36
p-value*	0.26	
Reduction phase		
	Omalizumab ***n=50***	**Placebo** ***n=45***
Number		
0	29 (58)	26 (58)
1	14	10
2	2	4
3	2	2
≥4	3	3
≥1	21 (42)	19 (42)
Median [range]	0 [0 – 10]	0 [0 – 10]
Mean	1.08	1.00
p-value*	0.85	

The same alternative methods of imputation as used in the analysis of exacerbations in inhaled corticosteroid users are shown in Table 102. In both of these analyses, as well as the protocol-defined one, there were more exacerbations in the omalizumab during the stable steroid phase, but the results were mixed during the steroid reduction phase.

Table 102. Trial 11: Sensitivity analyses of asthma exacerbations, oral corticosteroid group

	No imputation		Impute 1 additional	
Stabilization phase				
	Omalizumab *n=50*	**Placebo *n=45***	**Omalizumab *n=50***	**Placebo *n=45***
Number				
0	36 (72)	36 (80)	34 (68)	35 (78)
1	10	6	11	7
2	2	1	3	1
3	1	2	1	2
≥4	1	0	1	0
≥1	14 (28)	9 (20)	16 (32)	10 (22)
Median [range]	0 [0 – 4]	0 [0 – 3]	0 [0 – 4]	0 [0 –3]
Mean	0.42	0.31	0.48	0.33
p-value*	0.40		0.30	
Reduction phase				
	Omalizumab *n=47**	**Placebo *n=44****	**Omalizumab *n=50***	**Placebo *n=45***
Number				
0	30 (64)	27 (61)	29 (58)	26 (58)
1	13	10	17	12
2	2	4	2	4
3	2	1	2	1
≥4	0	2	0	2
≥1	17 (36)	17 (39)	21 (42)	19 (42)
Median [range]	0 [0 – 3]	0 [0 – 7]	0 [0 – 3]	0 [0 – 7]
Mean	0.49	0.73	0.54	0.76
p-value*	0.63		0.73	

*not the intent-to-treat population
*Generalized Cochran-Mantel-Haenszel (van Elteren) test using standardized midranks and controlling for dosing schedule

Comments

It is clear that there was no benefit to oral corticosteroid users during the stable steroid phase. During the steroid reduction phase a small number of subjects drove the mean count difference in the direction of a treatment benefit, and the small sample size contributed to the magnitude of the effects. However there was no treatment effect in the proportions of subjects with at least 1 exacerbation. Overall, the results show no notable benefit of omalizumab in the oral corticosteroid users.

- *Secondary endpoint: inhaled b-agonist use*

Inhaled corticosteroid users

Table 103 shows the mean puffs of β-agonist medication used per day at baseline and in periods of time between visits during both the stable steroid and steroid reduction phases (this parameter was measured more frequently during the steroid reduction period). Median use at the end of the treatment period was not as different between the treatment groups as the means (medians at week 32 : 0.48 omalizumab, 0.71 placebo). These results may be influenced by dwindling numbers of subjects at the end of the trial, with possible selection bias.

Table 103. Trial 011: Mean daily puffs (± std. dev.) of b-agonist for asthma control (inhaled corticosteroid users)*

		Omalizumab	Placebo
Baseline	*n*	*124*	*119*
		2.4 ± 3.7	2.2 ± 3.3
Weeks 4-8	*n*	*125*	*120*
		1.8 ± 3.3	2.3 ± 3.5
		p=0.16	
Weeks 12-16	*n*	*118*	*115*
		1.9 ± 3.8	2.2 ± 3.4
		p=0.33	
Weeks 22-24	*n*	*116*	*113*
		2.11 ± 4.0	2.5 ± 3.7
		p=0.28	
Weeks 30-32	*n*	*114*	*106*
		1.7 ± 3.2	2.4 ± 3.9
		p=0.06	

*see text for methods of imputation; selected time points shown
Note: Stable steroid phase is weeks 0-16; steroid reduction is weeks 16-32.

Comment

The extent of the benefit in b-agonist usage in the inhaled corticosteroid users was small in the inhaled corticosteroid users overall (between ½ and 1 puff per day) and similar to that seen in the critical efficacy trials. A difference of this magnitude is clinically not notable.

Oral corticosteroid users

Table 104 shows mean use of β-agonists in puffs per day at baseline and in periods of time between visits. Baseline use was greater in the omalizumab group. Use trended downward in the omalizumab group and trended upward in the placebo group (with a greater tendency during the steroid reduction phase). Median use was not as different at week 32 as means (2.8 omalizumab, 3.3 placebo). These results also may be influenced by dwindling numbers of subjects at the end of the trial, with possible selection bias.

Table 104. Trial 011: Mean puffs (± std. dev.) of b-agonist for asthma control (oral corticosteroid users)

		Omalizumab	Placebo
Baseline	*n*	*50*	*45*
		6.4 ± 8.3	5.1 ± 12.4
Weeks 4-8	*n*	*48*	*45*
		6.2 ± 8.6	5.8 ± 17.0
		p=0.10	
Weeks 12-16	*n*	*46*	*44*
		5.1 ± 7.5	5.5 ± 13.0
		p=0.74	
Weeks 22-24	*n*	*47*	*44*
		4.5 ± 5.6	5.9 ± 14.2
		p=0.91	
Weeks 30-32	*n*	*43*	*39*
		3.7 ± 4.9	6.5 ± 13.9
		p=0.35	

*Selected time points shown
Note: Stable steroid phase is weeks 0-16; steroid reduction is weeks 16-32.

Comments

Use of b-agonists in the inhaled corticosteroid users was minimally affected, a similar effect to that seen in the critical efficacy trials. The treatment effect was more pronounced in the oral corticosteroid users; however, the much smaller difference in median puffs compared to mean puffs at the end of the trial indicates that the means were influenced by a subset of subjects with relatively higher use in the placebo group.

- *Secondary endpoint: asthma symptoms*

Inhaled corticosteroid users

Symptom scores were similar at baseline at about 1.4; by the end of the steroid reduction period, mean scores dropped about 0.4 points in the omalizumab group and 0.1 in the placebo group on a scale of 0-9. Once again, results may be influenced by dwindling numbers of subjects (11 dropouts in omalizumab and 13 dropouts in placebo), with selection bias a possibility.

Oral corticosteroid users

A baseline difference existed between the groups at baseline (omalizumab worse than placebo). Although slightly worse than the scores in the inhaled corticosteroids users (group mean scores of about 2.3 and 1.7 in the omalizumab and placebo groups, respectively), the asthma symptom score among these oral corticosteroid users suggests reasonable control of symptoms at baseline. There was an insignificant difference at the end of the trial (scores of about 1.7 and 1.9, respectively). This is consistent with trends toward a common mean score.

- *Secondary endpoints: Lung function (spirometry)*

The following results were not examined in detail.

Inhaled corticosteroid users

- Morning peak expiratory flow from visit 4 (not baseline): Least squares mean PEFR was the same for both treatment groups (382 l/min) at visit 4. At the end of the stabilization period means were slightly higher in both groups (387 and 390 l/min, respectively). At the end of the steroid reduction phase the placebo group's mean was back to visit 4 values (382 l/min) and the omalizumab-treated group's mean was a little higher (391 l/min). The omalizumab group's mean increase from baseline is clinically not significant.

- FEV_1: Genentech states that there was little change in post-bronchodilator FEV_1 over time, and that neither group showed a deterioration during the steroid reduction phase.
- FVC and FEF_{25-75}: Genentech reports that there were no marked between-treatment differences in either trial period.

Oral corticosteroid users

- Morning peak expiratory flow from visit 4 (not baseline): Least squares mean PEFR was nearly the same for placebo and omalizumab treatment groups (322 and 321 l/min, respectively) at visit 4. At the end of the stabilization period means were still nearly the same (319 and 322 l/min, respectively). At the end of the steroid reduction phase the placebo group's mean was slightly lower (309 l/min) and the omalizumab-treated group's mean had remained the same (322 l/min). These mean differences are clinically unimportant.
- FEV_1: Review of FVC means at baseline, end of steroid stabilization period, and end of steroid reduction phase shows no notable differences during the trial for either treatment group.
- FVC and FEF_{25-75}: Genentech does not report on these results. Review of FVC means at baseline, end of steroid stabilization period, and end of steroid reduction phase shows no notable differences during the trial for either treatment group. Data were not reviewed for FEF_{25-75}.

Comment

As in the critical efficacy trials, there was no notable effect of omalizumab on spirometry or peak expiratory flow.

- *Secondary endpoint: global evaluations*

Examination of the distributions of the scores of excellent, good, moderate, poor, and worsening, showed that both investigators and subjects scored omalizumab better overall than placebo (Appendix Table 167).

Comments

The impression of treatment favored omalizumab more among the inhaled users. These scores are impressions of overall effect and do not specify what treatment effects are assessed by subjects or investigators. The results do not include the entire trial population, and the possibility of selection bias cannot be ruled out.

Concomitant medication use

During the treatment period use of non-steroidal antiasthmatic agents was generally comparable between treatment groups. However, there was a slight preponderance of omalizumab-treated subjects in the inhaled corticosteroid group who took the long-acting β-agonists salmeterol and formoterol (50% vs. 44%). These agents are used for long-term asthma control.

During the follow-up period, there were no striking differences in the use of major anti-asthmatic medications between subjects previously treated with placebo or omalizumab.

Comment

The small difference in numbers of subjects taking b-agonist controller medications may have slightly favored outcomes in the omalizumab group, but the effect would not be expected to be great.

Follow-up period evaluations

Corticosteroid doses

Proportions of subjects with use of various concomitant medications were comparable between the two groups formerly on placebo and omalizumab.

Table 105 shows doses of corticosteroid at baseline and end of the steroid reduction and followup periods. Final visit data were based on a slightly smaller set of subjects than started the trial, so the magnitude of the difference cannot be stated with any certainty at the final follow-up. However, the numbers of missing values was relatively small. Final corticosteroid doses were less than baseline values for both groups.

Table 105. Trial 011 Follow-up period: doses of corticosteroids (mg)

		Inhaled		Oral	
		Omalizumab	**Placebo**	**Omalizumab**	**Placebo**
Baseline	*n*	*126*	*120*	*50*	*45*
	Mean ± sd	1.38 ± 0.36	1.36 ± 0.36	10.0 ± 6.3	10.6 ± 6.7
	median	1.50	1.25	10.0	10.0
End of reduction	*n*	*126*	*120*	*50*	*45*
	mean ± sd	0.59 ± 0.51	0.77 ± 0.56	6.4 ± 12.3	4.7 ± 6.3
	median	0.50	0.75	3.1	2.5
		Former omlzmb	**Former placebo**	**Former omlzmb**	**Former placebo**
End of follow-up	*n*	*118*	*110*	*43*	*42*
	mean ± sd	0.78 ± 0.58	0.81 ± 0.47	6.1 ± 12.7	3.8 ± 4.7
	median	0.75	0.90	0	2.5

Comment

These data show that cessation of omalizumab did not result in a rebound in corticosteroid use.

Estimate of asthma exacerbation rates

To estimate the incidence of asthma exacerbations in the follow-up period Genentech selected the following terms from the adverse event data base: "asthma exacerbation," "exacerbation asthma," "asthma exacerbation due to infection," "severe asthma attack," and "asthma attack." Table 106 shows that the proportions of subjects with these terms was lower for omalizumab in the inhaled corticosteroid subgroup, but slightly higher in the former oral corticosteroid subgroup.

Table 106. Trial 011: Follow-up period exacerbations* by former treatment group

	Inhaled		Oral	
	Omalizumab	**Placebo**	**Omalizumab**	**Placebo**
	n=119	***n=113***	***n=46***	***n=42***
Subjects (n, %)	20 (17)	26 (23)	13 (28)	11 (26)
Exacerbations	21	34	17	18
Subjects with serious asthma exacerbations	0	1	2	1

* From examination of asthma-related terms in the adverse event data base

Comments

The rates/week of these adverse event-determined exacerbations in the inhaled corticosteroid users were from 1 ½ -2 times that of observed exacerbations during the steroid reduction phase (calculation not done for the oral corticosteroid-requiring group). While this calculation is based upon small numbers of exacerbations, it is consistent with the ascertainment of exacerbations that may not have required treatment with systemic corticosteroids. Thus these data

are not amenable to quantitative comparisons with the protocol-defined exacerbation rates. However, the data on serious exacerbations suggest that there is no significant rebound effect of the cessation of omalizumab.

Follow-up period spirometry (FEV_1, FVC, and FEF_{25-75}) mean data did not show any notable intertreatment group differences in differences from baseline to the end of the follow-up period.

Antibody

The antigenicity of omalizumab is discussed in a separate section of this review.

Summary: Efficacy in trial 011

In trial 011 subjects on inhaled corticosteroids treated with omalizumab were more able to decrease inhaled corticosteroid use compared to their placebo counterparts, as was shown in the critical efficacy trials 008 and 009, but not to as great an extent. This may have been due to their higher baseline usage compared to the subjects in trials 008 and 009, or other factors. The benefit of omalizumab was not extended in the small population on oral corticosteroids, however. Reductions in oral corticosteroids were not demonstrated.

Among inhaled corticosteroid users improvements in exacerbation rates were confined to the steroid reduction phase, and were dependent upon the imputation technique used. A treatment benefit was not seen during steroid stabilization. There was no benefit in exacerbation rates among subjects on oral corticosteroids.

Differences in symptom scores were minimal, as were differences in markers of pulmonary physiology. Use of rescue medication was decreased to a small extent in omalizumab subjects in both the inhaled and oral corticosteroid users.

Overall, this trial does not replicate in subjects on oral corticosteroids the treatment effects previously seen in subjects with modest use of inhaled corticosteroids, who were studied in trials 008-010.

OPEN-LABEL TRIALS

Trial Q2143g was a large (1899-subject) trial in which subjects were randomized 2:1 to open-label treatment with omalizumab at the proposed dose or to standard treatment. Because of its open-label nature it is primarily useful as a safety trial. However, because of its size, the fact that it captured exacerbation data, and its enrollment of subjects whose concomitant medications were more liberalized than those of trials 008-011, its results are worth examining. Trial IA04 was a non-IND trial that also randomized subjects 2:1 to omalizumab at the proposed dose or to standard treatment. It is also limited in that it too had an open-label design. However, its results are worth examining due to its enrollment of subjects who had worse control of asthma than seen in other trials submitted for efficacy considerations.

OPEN-LABEL TRIAL Q2143G

Title

Trial Q2143g was entitled "A multicenter, randomized, controlled, open-label study to evaluate the safety of Xolair in moderate to severe persistent asthma subjects already treated with other therapies (ALTO)."

Design

Q2143g was a multicenter, open-label 24-week trial conducted solely in the United States that was to randomize about 1500 subjects with asthma 2:1 to omalizumab or to no additional trial treatment. Its primary endpoint was an assessment of serious adverse events, but information was collected on asthma exacerbations and concomitant medications.

Comment

The estimation of efficacy in an open-label trial is problematic. However, the controlled design and the size of the trial make an examination of the results worthwhile. The results are shown to assess consistency or lack of consistency with blinded trials.

Objectives

The principal objective of Q2143g was to determine the safety of omalizumab in a population of subjects whose other medications were not as restricted as they were in the critical efficacy trials originally submitted to the BLA.

Trial treatments

Subjects either received no asthma treatment other than their usual asthma care, or were administered omalizumab in addition, at the proposed dose of a minimum of 0.016 mg/kg/IU/ml (IgE) over a 4-week period, divided into every-2-week dosing if the dose was greater than 300 mg. This was the same treatment regimen as used in the critical efficacy trials and trial 010. The dosing chart (Appendix Table 168) was modified from that used in trials 008-011 in that it more finely divided body mass increments at lower body masses, with a lower body mass limit (20 kg vs. 30 kg), allowing calculation of doses for subjects with higher serum IgE. It also provided a calculation for subjects in the upper and lower levels of body mass in the 90-150 kg category.

Concomitant medications

No restrictions were placed on treatment with concomitant medications.

Randomization and blinding

The trial was open-label; there was no blinding. Randomization was stratified by center and used permuted blocks.

Subject qualifications

The screening process was anticipated to take about 2 weeks. Subjects were to be randomized within 48 hours of visit 2. This could occur at any time during the 2 week screening period if a subject met qualifications.

Inclusion criteria

- Males or females, 6-75 years old
- Have a documented physician diagnosis of moderate to severe, persistent asthma, defined in the National Heart, Lung, and Blood Institute (NIH) guidelines as FEV, <80% predicted for height, age, and sex, or a history of FEV_1<80%
- Currently be receiving the following medications:
  --moderate doses (lower limit of dose defined; no upper limit) of any inhaled steroid preparation on a daily basis ≥30 days prior to screening
  and/or
  --oral steroids at a stable dose on a daily basis ≥30 days prior to screening
  and
  --currently be receiving at least one of the following drugs on a daily basis at a stable dose ≥30 days prior to screening: long-acting β-adrenergic (salmeterol), leukotriene receptor antagonist, theophylline, or sodium cromoglycate
- Serum IgE level ≥30 IU/ml and ≤1300 IU/ml
- Body weight ≥20 kg and ≤l50 kg
- Body/serum IgE product within dosing chart

Exclusion criteria (selected)

- Active asthma exacerbation requiring at least the doubling of inhaled steroid dose or the initiation or increase of oral steroids.
- Recent asthma exacerbation and not back to original dose of inhaled or oral corticosteroid for ≥30 days prior to screening
- Hypersensitivity to any ingredients of omalizumab, including excipients (sucrose, histidine, polysorbate 20)
- Aspirin or other nonsteroidal anti-inflammatory drug-induced asthma
- Active lung disease other than asthma
- Smoking within 2 years of the study screening visit or history of smoking ≥l0 pack years
- Significant systemic disease within the previous 3 months, including but not limited to hematological conditions such as disorders of coagulation or platelet dysfunction or any condition requiring anticoagulation
- Systemic condition requiring regular administration of immunoglobulin
- Previously randomization into Q2143g; history of noncompliance to medical regimens

Comments

Protocol specifications for asthma severity were not very different from those in the critical efficacy trials 008 and 009. The biggest difference between this trial and trials 008/009 was in the liberalization of concomitant medications.

The trial included subjects at a lower age than to be included in proposed labeling.

Procedures and evaluations

Unlike the critical efficacy trials and trial 011, there was no guidance to subjects or investigators for the recognition and treatment of worsenings of asthma.

The following is a list of the important procedures conducted at various phases of the trial.

Up to 2-week screening (visit 1)

- Spirometry
- Serum IgE
- Complete blood count with differential and platelets
- Demographics and history
- Limited physical examination
- Concomitant medication use

Treatment period

Visit 2, week 0, was the baseline visit. Subsequent visits were called visits 2a, 2b, and 3-5. They occurred at weeks 1, 2, 4, 12, and 24 after baseline.

All subjects followed the following procedures. Modifications to these common procedures for the different treatment groups are described below.

Visit 2 (baseline):

- Postrandomization adverse experiences
- Spirometry
- Vitals, height and weight
- Symptom assessment for the prior 14 days using a modified version of the Inner City Asthma Study Morbidity Assessment (ICASMA)
- Concomitant medication use

Visits 3 and 4 (weeks 4 and 12)

- Adverse experiences
- Spirometry
- Complete blood count with differential and platelets
- Vital signs, height and weight
- Symptom assessment for the prior 14 days using the ICASMA questionnaire
- Asthma exacerbations
- Concomitant medication use

Visit 5 (week 24) or early discontinuation

- Adverse experiences
- Spirometry
- Complete blood count with differential and platelets
- Vital signs, height and weight
- Symptom assessment using ICASMA questionnaire
- Asthma exacerbations
- Concomitant medication use

Omalizumab subjects received treatment starting at visit 2 and continuing until week 20 (for subjects on the Q4w schedule) or week 22 (for subjects on the Q2w schedule). Further additional procedures included:

Visits 2a and 2b (weeks 1 and 2) for omalizumab-treated subjects only

- Adverse experiences
- Complete blood count with differential and platelets

Visit 5

- Trough omalizumab concentration

Early termination visit

- Omalizumab concentration

In addition, omalizumab subjects were to be queried about adverse experiences at each injection visit.

After an amendment dated April 10, 2002, telephone calls for the elicitation of possible adverse experiences were instituted monthly between visits 3, 4, and 5. These additional queries were made after the trial had begun enrollment.

Analytical plan

Subjects were grouped according to the treatment actually received.

As a safety trial, the primary analytical population was a "safety population." Control subjects were included if they completed visit 2 (baseline); omalizumab-treated subjects were included if they had received at least 1 dose. No imputation was to be done for missing data.

Comments

The safety population excluded very small, and approximately equal, proportions of subjects in each treatment arm: 17/637 (2.7%) in control, and 41/1262 (3.2%) in the omalizumab group. The evaluation of efficacy using this population is not expected to be dramatically different from that in the intent-to-treat population.

Efficacy variables

- *1° endpoint*

The primary endpoint was based on the incidence of serious adverse events and there was no plan for inferential statistical analysis. As this is a safety endpoint, it will not be discussed in this document.

- *2° endpoints*

Secondary endpoints included:

- Asthma exacerbations, defined as:
  - --worsening of asthma at any time requiring an urgent (unscheduled) visit for medical care
  - --a visit to an emergency room for worsening of asthma symptoms
  - --hospitalization due to worsening of asthma

  and one or more of the following for asthma control:
  - --doubling of inhaled steroid dose
  - --an increase in dose of oral steroids
  - --inception of oral, IV, or subcutaneous steroids

The protocol specified analyses of each of the following categories of protocol-defined asthma exacerbations separately:

- --total
- --resulting in urgent (unscheduled) medical visit
- --resulting in visit to an emergency room
- --resulting in hospitalization

The statistical method was a Poisson regression model with adjustment for time on study, where time on study was the time in the treatment period less the time spent in exacerbations.. The method did not use imputation for early discontinuers.

- Nocturnal symptoms as measured by changes from baseline to visits 3-5 in the modified Inner City Asthma Study Morbidity Assessment (ICASMA). The modified ICASMA consisted of 6 questions that asked how asthma affected a subject's life within the last 14 days (5 questions) or nights (1 question). The nocturnal question was: "In the last 14

nights, how many nights did you or your child wake up because of asthma, wheezing or tightness in the chest, or cough?" The statistical method specified was a comparison of change from baseline using Wilcoxon rank-sum test.

Two interim analyses of platelet count data were performed, after enrollment of 79 and 458 omalizumab-treated subjects (reports dated in April and October 2001, respectively). The first was specified in a protocol amendment (see "Protocol modifications" section); the latter was not formally proposed. The effect of omalizumab on platelets is reviewed in the safety review of this submission.

Protocol modifications

The protocol was formally amended 4 times, all after the initiation of the trial on July 17, 2000. The following describes the major features of each amendment.

1. December 29, 2000: intensification of platelet monitoring subsequent to a report of thrombocytopenia induced in juvenile ---------- monkeys by omalizumab, and thrombocytopenia with hemorrhage and death induced by a related compound, ------. Subjects were excluded for thrombocytopenia but a previous exclusion for a history of significant systemic disease was removed. An interim platelet analysis was added. The as-treated population was instated as the primary analytical efficacy population.
2. June 5, 2001: The dosing table was revised to ensure proper dosing of subjects with body masses <125 kg and ≤150 kg and a baseline IgE level of >100 IU/ml and ≤300 IU/ml (raising the dose for these subjects); exclusions for subjects with need for immunoglobulin or condition requiring anticoagulation were added.
3. January 22, 2002: The trial enrollment was increased from 900 to approximately1500; the monthly telephone calls to control subjects were added (the protocol originally did not include these calls); the method for analyzing the incidence of protocol-defined asthma exacerbations was changed from the Wilcoxon rank-sum procedure to a Poisson analysis. Subjects with a history of neoplasia were excluded.
4. April 10, 2002: created eligibility criteria for open-label extension protocols.

Comments

In an open-label trial the analysis of endpoints that depend upon subjective criteria, including corticosteroid dose adjustments or determination of the occurrence of asthma exacerbations, is suggestive only. The changes made to the trial would not impair significantly the soundness of the trial's results.

Results: Conduct of the trial

Note: In this document, tables for trial Q2143g show control to the left of omalizumab.

Dates of the trial

The trial was initiated on July 17, 2000, and was completed on July 31, 2002.

Screening failures

Table 107 shows major reasons for failing to qualify for trial Q2143. Other reasons for failing to qualify for the trial were smoking history, withdrawal of consent, not on required entry medications (4% each), loss to follow-up (2%), active asthma exacerbation (1%), and weight >150 kg (2 subjects) and thrombocytopenia (2 subjects).

Compared to the critical efficacy trials 008 and 009, a higher proportion of the screened population were excluded due to IgE falling outside the qualifying range, both for below-limit and for above-limit serum IgE values. In trials 008 and 009, about 5% of subjects had IgE too low;

about 9-12% of subjects had an IgE that was over the limit for those trials (700 IU/ml, which is lower than the limit for Q2143g).

Table 107. Trial Q2143g: Screening failures at 10% incidence or greater*

Reason	Excluded (%) *n=1412*
Serum IgE <30	380 (27)
FEV_1>80%	237 (17)
IgE/weight combination outside dosing table	236 (17)
Serum IgE >1300	210 (15)
"Other"	135 (10)

* from CRO data; not verified as of 3/25/03

Enrollment by site

None of the 164 sites had a preponderance of subjects (Table 108). About one half of the sites enrolled 10 subjects or fewer.

Table 108. Trial 2143g: Enrollment by site

Number of subjects	Number of sites
1-5	39
6-10	45
11-15	35
16-20	21
21-25	18
26-29	4
32, 48	1, 1

Demographics and baseline characteristics

As Table 109 shows, demographics and baseline characteristics were well balanced between the omalizumab and placebo groups. Comparing the Q2w and Q4w groups, proportions of subjects in each category were within 5% of each other except for the proportions of "White" subjects (73% vs. 82%) and males (49% vs. 39%). Serum IgE at screening differed remarkably between the Q2w and Q4w groups (337 ± 190 vs. 101 ± 65 IU/ml), as would be expected.

Table 109. Trial Q2143g: Demographics and characteristics in safety population*

	Control *n=620*	Omalizumab *n=1221*
Age (yr.) mean ± sd	40 ±17	41 ±17
Age group (yr.)		
6–11	43 (6.9%)	85 (7.0%)
12–17	44 (7.1%)	82 (6.7%)
18–64	498 (80.3%)	969 (79.4%)
≥65	35 (5.6%)	85 (7.0%)
Sex		
Male	264 (42.6%)	523 (42.8%)
Female	356 (57.4%)	698 (57.2%)
Race/ethnicity		
White	481 (77.6%)	958 (78.5%)
Black	80 (12.9%)	146 (12.0%)
Asian or Pacific Islander	10 (1.6%)	26 (2.1%)
Hispanic	39 (6.3%)	77 (6.3%)
American Indian or Alaskan native	1 (0.2%)	3 (0.2%)
Other	9 (2%)	11 (0.9%)
IgE level (IU/ml) at screening mean ± sd	194 ± 177	193 ±173
FEV_1 % predicted mean (range)	75 (16-138)	76 (24-185)

*excludes 3% of subjects from those enrolled (see "Analytical plan" for discussion)

As Table 110 shows, history of medical care for asthma was similar between the treatment groups. Proportions of subjects in the two schedule groups were similar.

Table 110. Trial Q2143g: Subject history and characteristics

	Control	Omalizumab
Ever been to an ICU, *n*	*610*	*1207*
Yes	55 (9.0%)	97 (8.0 %)
Previously intubated or on ventilator, *n*	*606*	*1195*
Yes	50 (8.3%)	93 (7.8%)
Overnight hospital stay in past year, *n*	*611*	*1208*
Yes	66 (10.8%)	138 (11.4%)
Visited ER in past year, *n*	*602*	*1187*
Yes	116 (19.3%)	253 (21.3%)
Urgent office visit in past year, *n*	*598*	*1183*
Yes	268 (44.8%)	539 (45.6%)
Percent FEV_1 predicted group		
≤60%	130 (21.0%)	254 (20.8%)
>60% to <80%	236 (38.1%)	429 (35.1%)
≥80%	254 (41.0%)	538 (44.1%)

Comments

As in the critical efficacy trials, there were more females than males, and "White" subjects were the great majority. Also, as in the critical efficacy trials, there were few subjects at the extremes of age, with the great preponderance in the 18-64 year-old age range.

Considering hospitalizations, the population of Q2143g included asthmatic subjects with greater clinical severity of disease than in the critical efficacy trials (in trials 008 and 009 the proportions with hospitalization were 3% and 6%, respectively). The proportions of subjects who had been to an emergency room for treatment of asthma in the prior year were also higher in Q2143g (in trial 008, the proportions of subjects for omalizumab and placebo were about 11 and 15%, respectively; in trial 009, 13 and 11, respectively). However, mean predicted FEV_1 was a little higher in Q2143g than in the critical efficacy trials, where the means were 68-70% of predicted.

Subject disposition

Table 111 shows subject disposition for all randomized subjects. Reasons for discontinuation were evenly balanced between the every-2-week and every-4-week omalizumab treatment subgroups. There were moderate numbers of discontinuations, more in the omalizumab group, the difference mostly due to a small increase in discontinuations due to adverse experiences.

Table 111. Trial Q2143g: Subject disposition, all randomized subjects

	Control *n=637*	Omalizumab *n=1262*
Total discontinuations	71 (11%)	179 (14.2%)
Reason for discontinuation		
Adverse event	3 (0.5%)	34 (2.7%)
Lost to follow-up	16 (2.5%)	20 (1.6%)
Subject or guardian's decision	28 (4.4%)	67 (5.3%)
Physician's decision	3 (0.5%)	13 (1.0%)
Sponsor's decision	2 (0.3%)	5 (0.4%)
Protocol violation	19 (3.0%)	40 (3.2%)

The nature of the adverse experiences, which were not common but occurred in proportionately more omalizumab-treated subjects, was diverse. A small minority of these events, about 2 in the omalizumab group and 1 in the nontreated group, were related to either "asthma exacerbation" or "shortness of breath."

Dosing and eligibility violations

One control subject was randomized to omalizumab but did not receive the product. Dosing errors were rare, occurring in 43 (3.4%) of all omalizumab-treated subjects.

Table 112 shows eligibility violations that by their nature could potentially affect efficacy. The proportions of subjects with these violations was similar in the Q2w and Q4w groups.

Table 112. Trial Q2143g: Selected eligibility violations in all randomized subjects (% of group)

	Control *n=637*	Omalizumab *n=1262*
FEV_1 >80%	13 (2.0)	39 (3.1)
History of COPD/bronchitis	2 (0.3)	6 (0.5)
IgE level outside of range (30–1300 IU/ml)	5 (0.8)	4 (0.3)
Not on qualifying medications	38 (6.0)	76 (6.0)
History of smoking	11 (1.7)	20 (1.6)

A protocol deviation that occurred in a modest number of subjects overall was lack of FEV_1 reproducibility. This measure was assessed as being acceptable if the largest 2 values assessed at a

given visit were within 5% of each other. This measure fell outside the limit in about 20% of subjects overall, but was balanced between treatment groups.

Comments

Eligibility violations were uncommon and well-balanced between treatment groups. Violations of FEV_1 reproducibility would tend to make the determination of effect on FEV_1 less reliable, but due to their extent in this trial would not be expected to influence the general trend in the results.

Exposure to product and duration in trial

The great majority of omalizumab-treated subjects received the protocol-required twelve Q2w doses or six Q4w doses (Table 113). The majority of the rest received fewer doses.

Table 113. Trial Q2143g: Numbers of doses received, omalizumab safety population

Number of Doses Received	Q2wk *(n= 476)*	Q4wk *(n= 745)*
1–2	26 (5.5%)	43 (5.8%)
3–5	14 (2.9%)	42 (5.6%)
6	4 (0.8%)	640 (85.9%)
7–8	11 (2.3%)	20 (2.7%)
9–11	21 (4.4%)	0
12	395 (83.0%)	0
>12	5 (1.1%)	0

The majority of subjects in both treatment arms spent from 24-28 weeks in the trial, with the majority of the remainder spending from 20-24 weeks in the trial. Table 114).

Table 114. Trial Q2143g: Subject duration in trial (safety population)

Weeks	Control *n=620*	Omalizumab *n=1221*
<20	44 (7%)	111 (9%)
20 - <24	165 (27%)	233 (19%)
24 - <28	395 (64%)	862 (71%)
28 - <40	16 (3%)	15 (1%)

Comments

Compliance to dosing and eligibility requirements in the trial was very good; compliance to complete participation was good.

Results: Efficacy

Primary endpoint

The primary endpoint of this trial was the incidence of serious adverse events. Safety is not reviewed in this document.

Secondary endpoints

Secondary endpoint: asthma exacerbations

Table 115 shows a summary of protocol-defined asthma exacerbations in the safety population. Although the protocol specified that the method would calculate time at risk as time in a

period less the time spent in exacerbations, Genentech additionally analyzed the results using a more appropriate definition. In this analysis, presented below, time at risk is time during a given period without subtracting time spent in exacerbations. The analysis excluded subjects with no recorded duration of an exacerbation. Since rates of exacerbations were calculated differently from the methods used in prior trials, comparisons of rates between this trial and previous ones cannot be done reliably; however, treatment differences within this trial would still be evaluable.

Table 115. Protocol-defined asthma exacerbations, safety population*

Asthma Exacerbation Endpoint	Control *(n=607)*	Omalizumab *(n=1207)*
Subjects with ≥1 asthma exacerbation	170 (28.0%)	260 (21.5%)
Exacerbation rate (per 24 weeks)	0.44	0.35
Exacerbation rate difference and 95% CI	-	-0.09 (-0.17 to 0.00)
Subjects with ≥1 hospitalization due to an asthma exacerbation	19 (3.1%)	27 (2.2%)
Hospitalization rate (per 24 weeks)	0.041	0.027
Hospitalization rate difference and 95% CI	-	-0.01 (-0.04 to 0.01)
Subjects with ≥1e.r. visit due to an asthma exacerbation	21 (3.5%)	35 (2.9%)
ER visit rate (per 24 weeks)	0.047	0.04
ER rate difference and 95% CI	-	-0.01 (-0.04 to 0.02)
Subjects with ≥1 one urgent clinic visit due to an asthma exacerbation	155 (25.5%)	239 (19.8%)
Urgent visit rate (per 24 weeks)	0.38	0.31
Urgent visit rate difference and 95% CI	-	-0.07 (-0.15 to 0.01)

* the population for this analysis excluded subjects with no recorded duration of an asthma exacerbation

Comment

The analytical method for calculating exacerbation rates in this trial is not the same as used in the critical efficacy trials 008-010. CBER calculated the observed exacerbation rates using the same method as shown in trial 011 and the critical efficacy trials (Table 116). This shows that the mean rates are comparable using the older method and the method used in Q2143g. The placebo frequency of subjects with at least 1 exacerbation in the stable steroid phases of trials 008 and 009 was about 18-23%, that in omalizumab-treated subjects, 10-11%. The current trial had higher rates, even considering that observation period was roughly 1½ times as long. The intertreatment difference in rates is comparable.

Table 116. Trial Q2143g: Observed asthma exacerbations (safety population)

	Omalizumab *n=1207*	Placebo *n=607*
Number (%)		
0	947 (78)	437 (72)
1	175 (14)	110 (18)
2	46 (4)	39 (6)
3	21 (2)	13 (2)
≥4	18 (1)	8 (1)
≥1	260 (22)	170 (28)
Median [range]	0 [0 – 6]	0 [0 – 5]
Mean	0.34	0.43
p-value*	0.002	

*CMH test adjusted for dose schedule differences

In Q2143g the proportions of subjects with asthma exacerbations requiring hospitalization or emergency room visits was very small, and the intertreatment differences correspondingly small.

Sensitivity analysis (CBER)

Table 117 shows CBER's analyses of subjects with different numbers of exacerbations, without imputation, using the safety population (Genentech's method also used only observed exacerbations). Imputation of a single exacerbation lowered the effect size slightly, due to the greater number of discontinuations in the omalizumab group.

Table 117. Trial Q2143g: Distribution of observed asthma exacerbations in safety population

	Impute 1 additional	
	Control *n=607*	**Omalizumab *n=1207***
Number (%)		
0	403 (66)	843 (70)
1	133 (22)	262 (22)
2	50 (8)	57 (5)
3	12 (2)	24 (2)
≥4	9 (1)	21 (2)
≥1	204 (34)	364 (30)
Median [range]	0 [0 – 5]	0 [0 – 6]
Mean	0.51	0.45
p-value*	0.089	

*CMH test adjusted for dose schedule differences

Subgroup analyses (Genentech)

Genentech presents an analysis of exacerbation rates among subjects with and without past skin test reactivity. The latter group included subjects who had no reactivity based on testing to a subset of the 5 common allergens used for testing. Genentech acknowledges, "the number of subjects known negative to all five allergens is too small (19 receiving Xolair, 5 receiving control) to support reliable analyses."

Upon request Genentech provided an analysis of exacerbations conducted similarly to that shown in Table 115, but for the population in proposed labeling, that is, ≥12 years old. The results (not shown in this review) were similar to those of the entire trial population. This is not surprising, considering that the requested analysis excluded <10% of subjects.

Subgroup analyses (CBER)

CBER compared the proportions of subjects with at least 1 exacerbation by treatment arm, using observed exacerbations only in various subgroups of race, FEV_1, age, IgE level, and body weight, as well as by sex (Appendix Table 169). The effect was not lost in any subgroup.

Secondary endpoint: nocturnal asthma symptom score

Table 118 shows the results of the nocturnal awakening scores. Subjects were questioned about the number of nights in the last 14 nights that there was an awakening due to asthma, wheezing, or tightness in the chest, or cough. Baseline values were similar. Scores trended downward for both groups, more in the omalizumab group.

Table 118. Trial Q2143g: Nocturnal awakening scores, safety population

		Control	Omalizumab
Week 0	*n*	*618*	*1220*
	Mean ± sd	2.19 ± 4.13	1.95 ± 3.79
	Subjects with ≥1	223 (36)	456 (37)
Week 4	*n*	*597*	*1182*
	Mean ± sd	2.13 ± 4.10	1.28 ± 2.95
	Subjects with ≥1	211 (35)	359 (30)
Week 12	*n*	*580*	*1124*
	Mean ± sd	1.88 ± 3.89	1.08 ± 2.71
	Subjects with ≥1	201 (35)	296 (26)
Week 24	*n*	*564*	*1080*
	Mean ± sd	1.80 ± 3.76	1.08 ± 2.76
	Subjects with ≥1	184 (33)	275 (25)

The median at all visits in both groups was 0; the range of scores at all visits in both groups was 0-14. Scores between the two treatment schedules were not remarkably different.

Comment

The reliability of symptom scores in an open-label trial is generally poor. The extent to which knowledge of treatment assignment affects nocturnal awakenings is unknown.

Tertiary endpoints

The following endpoints were not examined in any detail. They are summarized, for the safety population.

FEV_1, % predicted

Mean percent predicted FEV_1 was similar between the two groups at baseline (see baseline characteristics). At the end of the trial, mean percent predicted FEV_1 in the control group was 75 and that in the overall omalizumab group was 77. There was very little difference between the two groups.

FVC, % predicted

Mean percent predicted FVC at baseline was 88 in the control group and 89 in the overall omalizumab population. These values did not change notably at the end of the trial.

FEF_{25-75}, % predicted

Mean percent predicted FEF_{25-75} at baseline was 53 in the control group and 54 in the overall omalizumab population; at the end of the trial they were 60 and 63, respectively. There was no notable difference between the treatment groups in the change from baseline.

PEFR

Mean peak expiratory flow rate was 355 l/min in the control group and 358 in the overall omalizumab group at baseline. Both groups' changes from baseline to the end of the trial were slight: end of trial mean values for the control group were 360 l/min; for the overall omalizumab group, 368 l/min.

Daytime asthma symptom score

Subjects were given a questionnaire that assessed how many days in the previous 14 days various categories of symptoms occurred (cough or wheeze, slowing or stopping of activity, missed school or work days, changes in plans, or limitations of activity. Baseline mean scores were similar. Omalizumab-treated subjects had lower scores in most measures at the end of the trial (Appendix Table 170). However, the reliability of questionnaire data in an open-label trial is poor.

Concomitant medication use

Review of concomitant medication use showed no remarkable differences between treatment groups in medications used to treatment asthma. Table 119 shows proportions of subjects taking anti-asthma drugs during the trial if at a frequency of 10% or greater.

Table 119. Trial Q2143g: Subjects with use of anti-asthma medications (frequencies of 10% or greater per group) in safety population

Drug Class*/Generic Name	Control (n=620)	Overall Omalizumab (n=1221)
Antihistamines	379 (61.1%)	734 (60.1%)
Cetirizine hydrochloride	91 (14.7%)	184 (15.1%)
Fexofenadine hydrochloride	102 (16.5%)	212 (17.4%)
Loratadine	102 (16.5%)	187 (15.3%)
Bronchodilators and anti-asthmatics	610 (98.4%)	1208 (98.9%)
Albuterol/albuterol sulfate	455 (73.4%)	873 (71.5%)
Fluticasone propionate/salmeterol xinofoate	294 (47.4%)	548 (44.9%)
Ipratropium bromide	71 (11.5%)	118 (9.7%)
Salmeterol xinafoate	311 (50.2%)	625 (51.2%)
Theophylline	81 (13.1%)	165 (13.5%)
Leukotriene receptor antagonists	347 (56.0%)	657 (53.8%)
Montelukast sodium	285 (46.0%)	546 (44.7%)
Zafirlukast	66 (10.6%)	116 (9.5%)
Steroids	549 (88.5%)	1095 (89.7%)
Budesonide	144 (23.2%)	301 (24.7%)
Fluticasone propionate	354 (57.1%)	697 (57.1%)
Mometasone furoate	77 (12.4%)	144 (11.8%)
Prednisone	182 (29.4%)	329 (26.9%)
Triamcinolone acetonide	67 (10.8%)	122 (10.0%)
Allergenic extracts	70 (11.3%)	144 (11.8%)

*Totals in drug class refer to all use, not only those at 10% or greater

Comment

Use of controller medications, particularly leukotriene receptor antagonists and the long-acting b agonist salmeterol, was common in both groups.

Antibody

Antibody development was not assessed in this trial.

Summary: Trial Q2143g

Q2143g was a well-conducted trial that enrolled subjects with more liberalized use of concomitant medications. The subject population had a slightly higher tendency to have required intensive medical attention in the prior year than in the critical efficacy trials. Many subjects used concomitant medications (leukotriene antagonists and long-acting β-agonists) during the trial, which may have reduced the ability to detect exacerbations as a signal. In addition, efficacy assessments in an open-label trial are not reliable, given the possibility of bias in subjects' and investigators' assessments. Given this marked limitation, the results were consistent with the results of the blinded trials (critical efficacy trials and trial 011).

OPEN-LABEL TRIAL IA04

Title

Trial IA04 was entitled "A 52-week randomized, open-label, controlled, multi-center study to evaluate efficacy and tolerability of subcutaneous administration of omalizumab in subjects with poorly controlled moderate to severe allergic asthma in a naturalistic setting."

Design

Trial IA04 was conducted without FDA involvement (it was conducted outside the IND process). It was designed as a multicenter, 5-European country trial of 300 subjects with asthma aged 12-75 years old randomized 2:1 to omalizumab or to no additional trial treatment. After a 4-week screening period, subjects were randomized into a treatment period of 52 weeks, with a final visit 4 weeks afterwards. The primary endpoint was deteriorations of asthma.

Comments

The estimation of efficacy in an open-label trial is problematic. However, the controlled design, the duration of observation (1 year), and the increased asthma severity of the enrolled trial population, make an examination of the results worthwhile. The results are shown to assess consistency or lack of consistency with blinded trials.

Objectives

The primary objective of trial IA04 was to determine the effect of omalizumab on asthma deteriorations (which may or may not have required corticosteroids). Secondary objectives included other efficacy parameters, including systemic corticosteroid-requiring exacerbations, and safety.

Trial treatments

Subjects either received no asthma treatment other than their usual asthma care, or were administered omalizumab in addition, at the proposed dose of a minimum of 0.016 mg/kg/IU/ml (IgE) over a 4-week period, divided into every-2-week dosing if the dose was greater than 300 mg (Table 14). This was the same regimen as used in the critical efficacy trials.

Concomitant medications

Depot corticosteroids, immunotherapy, and investigational treatments were not permitted.

Randomization

Subjects were randomized to either omalizumab or to no additional treatment in a 2:1 ratio at visit 2. The subjects were randomized in blocks within each center.

Subject qualifications

The following lists the important inclusion and exclusion criteria for trial IA04.

Inclusion criteria

- Males or females, 12-75 years old
- Moderate persistent to severe persistent "allergic" asthma according to 1997 NHLBI Guidelines for at least 2 years
- ≥1 asthma-related hospitalization or emergency room visit and "at least one additional course of oral corticosteroid due to asthma in the previous year"
- For non-pediatric population: ≥800 µg daily dose beclamethasone dipropionate or equipotent dose of inhaled corticosteroid within the past 3 months

- For pediatric population: ≥400 µg daily dose beclamethasone dipropionate or equipotent dose of inhaled corticosteroid within the past 3 months
- Positive skin prick test to at least 2 "clinically relevant" allergens
- >12% improvement in FEV_1 over baseline with inhalation of β-agonist, documented within the past 6 months or at screening
- Serum IgE ≥30 IU/ml and ≤700 IU/ml
- Suitable weight for dosing

Exclusion criteria

- Hypersensitivity to any ingredients of omalizumab or "related drugs (e.g., monoclonal antibodies, polyclonal gamma globulin)"
- History of smoking >10 pack years
- Active lung disease other than allergic asthma
- Immunocompromise (e.g., lymphoma, AIDS, Wiskott-Aldrich, X-linked agammaglobulinemia
- Elevated serum IgE for reasons other than atopy
- Clinically significant disease or laboratory "profile" or any condition that might compromise the subject's safety, compliance, interfere with evaluations, or preclude completion of the trial, in the judgment of the investigator
- Depot corticosteroids within the 30 days prior to screening
- Desensitization immunotherapy
- Investigational treatment within the 30 days prior to screening
- Any condition that in the opinion of the investigator would render the subject ineligible for the trial schedule
- Platelet count below 130 x 10^9/l
- (in France only) history of suspected or confirmed autoimmune thrombocytopenia

Comment

Compared with the critical efficacy trials 008 and 009, protocol IA04 was designed to enroll subjects with a greater degree of asthma severity and did not place stringent limits on medications used to treat asthma.

Procedures and evaluations

The following is a list of the important procedures during the trial. After randomization, subjects were evaluated infrequently, but did return to sites every 2 or 4 weeks for their injections. The period of evaluation (without a programmed steroid reduction) was longer than the periods in either of the other two trials reviewed in this document.

4-week screening period (visit 1)

- Demographics and medical history; check inclusion and exclusion criteria
- Physical examination; CBC/diff/platelets, electrolytes and chemistries, urinalysis
- Skin prick test (or serum specific IgE test in the case of severe skin disease)
- FEV_1 reversibility test if not performed within 6 months prior to screening
- FEV_1; ECG
- Total and free IgE

Week1 (randomization, visit 2)

- FEV_1
- Inclusion and exclusion criteria check
- Adverse experiences and concomitant medications
- Assign randomization number

- Asthma questionnaire and asthma symptom score
- Distribute diary cards, instruct on use

Weeks 1 and 2 (omalizumab only)

- Platelet determinations

Weeks 14, 27, and 40 (visits 3-5)

- FEV_1
- Asthma questionnaire; asthma symptom score
- Adverse experiences and concomitant medications
- Collect and distribute diary cards

Week 53 (visit 6, end of "core period")

- FEV_1
- Physical examination; CBC/diff/platelets, electrolytes and chemistries, urinalysis
- Adverse experiences and concomitant medications
- Asthma questionnaire and asthma symptom score
- Collect and distribute diary cards

Week 57 (visit 7, follow-up)

- FEV_1
- Adverse experiences and concomitant medications
- Asthma questionnaire and asthma symptom score
- Collect diary cards

Diary cards contained information regarding concomitant medications, any day with oral corticosteroid or antibiotic use due to asthma, and the number of puffs of a short-acting β-agonist for as-needed use for asthma. The diary was completed each morning with reference to the previous 24 hours.

Management of exacerbations

The protocol did not contain detailed guidelines for the management of exacerbations.

Analytical plan

Efficacy variables

1° endpoint

The primary endpoint was determined using "asthma deterioration related incidents," defined as at least one of the following, due to asthma:

- course of antibiotic (minimum of 2 days)
- course of oral corticosteroid (minimum of 2 days)
- work or school missing day
- unscheduled physician visit
- emergency room visit
- hospital stay

The end of an asthma deterioration-related incident was defined by absence of all above events for ≥2 consecutive days. If a subject were on maintenance corticosteroids, queries could be made to determine that an increase was the result of a deterioration.

The protocol specified that the analytical population was all randomized subjects who received trial medication and from whom at least one efficacy measurement was obtained, excluding subjects who had not completed the trial schedule. However, the report of the trial states that the analytical population was all randomized subjects. This analysis in fact excluded 1 subject who was randomized in error, and one subject was dropped from analysis because of an asthma-related deterioration that lasted the duration of the trial.

The statistical method specified was a Poisson regression model with adjustment for time on study, where time on study was the time in the treatment period less the time spent in exacerbations. An imputation scheme was not specified in the protocol. The primary imputation method stated in the final report was to attribute an additional deterioration to subjects who discontinued if a deterioration had not occurred within 7 days of the discontinuation; if it were found, the deterioration was assumed to be the cause of the discontinuation, and an additional one was not imputed. Imputed exacerbations were given a duration of 0.

2^o endpoints

The protocol specified 9 secondary variables. The first 6 variables were:

1. The number of derived asthma exacerbation episodes over a 1-year period
2. Number of days with oral corticosteroids due to asthma
3. Number of days of absenteeism from school/work (significantly reduced performance for non-working subjects, as judged by the subject) due to asthma
4. Number of days with unscheduled physician visit due to asthma
5. Number of days with emergency room visit due to asthma
6. Number of days admitted in hospital due to asthma

Asthma exacerbations met protocol criteria if they were treated with systemic corticosteroids, and a minimum of 7 days were to elapse between episodes. The determination of these events required retrospective analysis of subject records.

The number of asthma exacerbation episodes requiring treatment with systemic corticosteroids was projected to a rate over a 1-year period, and analyzed similarly to the primary endpoint.

Comments

The definition of asthma deterioration incidents included potentially many degrees of severity. Conceivably a deterioration incident might have not required any change in the medical management. The addition of the secondary variable, asthma exacerbations treated with systemic corticosteroids, gave the trial an ability to determine a clear endpoint with some significance to subjects. However, the fact that these exacerbations were determined retrospectively is a significant drawback, since retrospective interpretation of the data was required. The interpretation of these endpoints can only be considered exploratory.

Interim analysis

An interim analysis of all data, including the primary endpoint, was scheduled for a time when all subjects had been in the trial for 6 months. Novartis employees were allowed to see the results. The significance level for the primary endpoint at the final analysis was set at 4.99%.

Comment

As the ability to assess efficacy in an open-label trial is subject to question, the impact of an interim analysis is relatively slight.

Protocol modifications

The original protocol was dated March 21, 2000. It was modified 4 times after enrollment of the first subject (see dates of the trial, in "Results"). The following describes the major features of each amendment.

1. May 30, 2000: This amendment allowed substitution of serum specific IgE testing for skin testing in subjects with long-term corticosteroid treatment or severe skin disease
2. September 8, 2000. Due to preclinical data on the effects of omalizumab on platelets, this amendment added the platelet count exclusion criterion and additional platelet monitoring

for subjects on omalizumab. It allowed for use of FEV_1 reversibility tests and skin prick tests performed 6 months prior to screening.

3. December 6, 2000: This amendment added a platelet determination at 1 and 2 weeks after the first administration of omalizumab. It allowed screening tests performed more than 3 months prior to visit 2, with some exceptions.

3a. February 5, 2001: This amendment was valid in France only. It excluded subjects with a history of autoimmune thrombocytopenia, even if only suspected, and added more platelet determinations.

4. November 14, 2001: This amendment added the secondary outcome variable based on asthma exacerbations requiring treatment with systemic corticosteroids. The statistical analysis of the primary endpoint was changed from either an ANCOVA or a Wilcoxon rank-sum to a Poisson regression. In addition, the interim analysis, which had been designated to an independent board, was designated as now being the province of Novartis employees. A prior plan to adjust the level of significance at the final analysis was discarded (however, this was later reinstated).

Comments

The amendments would not be expected to have had a detrimental effect on the overall judgment of the effect of omalizumab in this trial. The recording of asthma exacerbations retrospectively renders this endpoint subject to even more bias in an open-label trial than in blinded one, rendering conclusions about this endpoint somewhat problematic.

Results: Conduct of the trial

Note: As for all trials except trial Q2143g, tables in this document show control to the right of omalizumab.

Dates of the trial

The first subject was recruited on May 25, 2000; the last subject completed the trial on May 9, 2002.

Screening failures

Genentech did not collect data on screening failures.

Enrollment by site

Table 121 shows that no site of the 49 enrolled a predominating number of subjects. About one half of the sites enrolled 5 or fewer subjects.

Table 120. Trial IA04: Enrollment by site

Number of subjects	Number of sites
1-5	25
6-10	15
11-15	7
18	2

Demographics and baseline characteristics

Table 121 shows that demographics of the enrolled population were similar to those of the other trials reviewed in this document. Females predominated, and the great majority of subjects were Caucasian. Height was well matched (not shown); weight was not determined in the control group.

Table 121. Trial IA04: Demographics (ITT population)

	Omalizumab n=206	**Control n=106**
Sex		
Male	58 (28.2)	34 (32.1)
Female	148 (71.8)	72 (67.9)
Race		
Caucasian	199 (96.6)	100 (94.3)
Black	4 (1.9)	1 (0.9)
Oriental	2 (1.0)	3 (2.8)
Other	1 (0.5)	2 (1.9)
Age (yr.)		
Mean range	38.2 12 - 73	39.3 12 – 71

Table 122 shows that the subjects in trial IA04 generally needed more intensive medical attention than those in the critical efficacy trials and the other asthma trials reviewed in this document. About 40% of subjects in both groups were hospitalized at least once in the prior year due to asthma.

Table 122. Trial IA04. Subject characteristics (ITT population)

	Omalizumab *n=206*	**Control *n=106***
GINA(1998) treatment step n(%)*		
Step 1	1 (0.5)	0
Step 2	0	0
Step 3	161 (78.2)	88 ((83.0)
Step 4	44 (21.4)	18 (17.0)
%Predicted FEV_1 mean(SD) *n*	71.4(21.4) *204*	71.6(21.9) *105*
Mean (SD) serum IgE - IU/ml	204(153)	not done
Emergency room visits, prior yr.		
No. (%) with ≥ 1 visit	186(90.3)	97(91.5)
Mean(SD) visits/subject	2.6(3.29)	2.5(3.61)
Hospitalizations due to asthma, prior yr.		
No. (%) with ≥ 1 hospitalization	87(42.2)	48(45.3)
Mean(SD) hospitalizations/subject	0.7(1.31)	0.9(2.05)
Courses of oral corticosteroids, prior yr.		
No. (%) with ≥ 1course	206(100.0)	105(99.1)
Mean(SD) courses/subject	3.7(3.56)	3.4(3.35)
BDP** equivalences at baseline(μg), Median (min-max)	2,000(0-10,000)	2,000(400-8,000)

*beclamethasone dipropionate, an inhaled corticosteroid

**Global Initiative for Asthma: see Appendix Table 171 for GINA 1998 treatment steps

The submission classifies about 94% of the subjects in this trial as "severe persistent," based upon adapted GINA criteria for the presence of symptoms accompanying various intensities of treatment using symptom collections from questionnaires. The validation of this method of adaptation is not presented.

Table 123 shows details of the medications that were used at baseline. The two treatment arms were comparable; the great majority of subjects were on inhaled corticosteroids and long- or short-acting β-agonist medications.

Table 123. Trial IA04: Baseline use of medications (subjects, %)

	Omalizumab	Control
Medication	***N=206***	***N=106***
Anti-cholinergics	22 (10.7)	11 (10.4)
Anti-histamines	10 (4.9)	7 (6.6)
Anti-leukotrienes	60 (29.1)	30 (28.3)
Corticosteroids		
Inhaled	205 (99.5)	106 (100.0)
Systemic	47 (22.8)	19 (17.9)
β-agonists		
Long-acting	160 (77.7)	83 (78.3)
Short-acting	192 (93.2)	98 (92.5)
Xanthines + Xanthine derivatives	43 (20.9)	19 (17.9)

Subject disposition

Table 124 shows that the a substantial proportion (22% overall) of subjects discontinued from the trial and that the discontinuation rate in the control group was nearly twice that of the omalizumab-treated group. The principal reason for withdrawal in the placebo group was withdrawal of consent. A much larger proportion of omalizumab-treated subjects discontinued due to adverse experiences.

Table 124. Trial IA04: Subject disposition (ITT population)

	Omalizumab	Control
Randomized	206 (100.0)	106 (100.0)
Discontinued	35 (17.0)	33 (31.1)
Adverse event(s)	15 (7.3)	1 (0.9)
Protocol violation	2 (1.0)	2 (1.9)
Subject withdrew consent	9 (4.4)	18 (17.0)
Lost to follow up	6 (2.9)	11 (10.4)
Administrative problems	2 (1.0)	1 (0.9)
Death	1 (0.5)	0

Comment

The large proportion of subjects who discontinued from this trial makes the interpretation of the efficacy results problematic, due to uncertainties over the possible outcomes of subjects who dropped out.

Eligibility and dosing violations

Three subjects in each treatment arm were enrolled with an active or ongoing excluded medical history; 1 subject (omalizumab-treated group) was enrolled without a qualifying skin test, 1 subject (omalizumab-treated group) was enrolled who did not have a qualifying hospitalization or emergency room visit and an additional course of oral corticosteroids. Ten subjects overall (9 omalizumab and 1 control) did not have a qualifying FEV_1 reversibility test. The largest single dosing violation was in doses received more than 3 days after the scheduled dose (125 subjects for a total of 243 times, all in the omalizumab group); the second most common was subjects who missed a dose (22 subjects).

Comments

Eligibility violations were rare. Dosing violations were rare or not likely consequential: the total number of doses given in the trial was 3379, so the percent of doses not given on time was 7%. This would not likely have had a significant impact on the effect of omalizumab in this trial.

Duration of trial participation

Trial participation was good. The majority of subjects (76% of the omalizumab group and 66% in the placebo group) were exposed to omalizumab or were in the trial for from 52-60 weeks. Median participation in the trial was 56 weeks in both treatment arms. However, when considered in 4-week intervals, the largest proportions of subjects discontinued from the trial in the first 4 weeks, when a much higher proportion of control subjects discontinued participation (17% of control, and 5% of omalizumab subjects).

Interim analysis

One interim analysis of efficacy data was performed, at a time when all randomized subjects had been on the trial for 6 months.

Comment

The performance of an interim analysis in an open-label trial, whose analysis is not expected to be blinded, is not a critical issue.

Results: Efficacy

Primary endpoint

Table 125 shows the occurrence of asthma-related deteriorations as submitted. These analyses were performed on a so-called "supporting ITT population," which consisted of all randomized subjects from whom at least 1 diary card had been obtained.

Table 125. Trial IA04: Subjects (%) with asthma-related deteriorations*

Number of deteriorations	**Omalizumab N=191**	**Control N=89**	**Omalizumab N=191**	**Control N=89**
	Imputation		No imputation	
0	69 (36)	18 (20)	75 (19)	21 (24)
1	44 (23)	12 (14)	39 (20)	9 (10)
2	23 (12)	12 (14)	23 (12)	12 (14)
3	9 (5)	5 (6)	9 (5)	7 (8)
4	11 (6)	10 (11)	10 (5)	8 (9)
5-10	23 (12)	19 (21)	23 (12)	19 (21)
> 10	12 (6)	13 (15)	12 (6)	13 (15)
≥1	122 (64)	71 (80)	116 (61)	68 (76)
p-value	<0.001		<0.001	

*Subjects with at least 1 diary card

Comments

Since the primary endpoint was presented on a subset of the subjects (not the ITT population), the inter-treatment group analysis is expected to be somewhat inaccurate.

Examining observed events only in the ITT population, without imputation, the intertreatment group difference in the number of subjects with ³1 asthma deteriorations was about half that shown in Table 125: 116 (56%) in the omalizumab-treated group as compared to 68 (64%) in the control group.

Because the clinical meaning of asthma deterioration incidents is diverse, the focus of this review is on the analysis of systemic corticosteroid-requiring asthma exacerbations to follow.

Secondary endpoints

Secondary endpoint: protocol-defined asthma exacerbations

Table 126 shows the submitted analysis of protocol-defined asthma exacerbations. The protocol defined an asthma exacerbation as a deterioration of asthma requiring systemic corticosteroids, determined from review of subject records. Treatment favored omalizumab in this analysis. The annualized rates of exacerbations in the placebo group was 2.9; in the omalizumab group, 1.1.

Table 126. Trial IA04: Subjects (%) with protocol-defined asthma exacerbations (ITT population) with imputation

Number of exacerbations	**Omalizumab N=206**	**Control N=106**
0	102 (49.5)	28 (26.4)
1	62 (30.1)	33 (31.1)
2	24 (11.7)	17 (16.0)
3	9 (4.4)	8 (7.5)
4	6 (2.9)	4 (3.8)
> 5	3 (1.5)	16 (15.1)
≥1	104 (50.5)	78 (73.6)
p-value*	<0.001	

*Cochran-Mantel –Haenszel test for the proportions with or without protocol-defined exacerbations was <0.001.

Comments

The retrospective nature of the analysis of exacerbations, especially in an open-label trial, renders attempts to generate firm conclusions about these results problematic. However, these results can be seen as somewhat supportive, in a population somewhat more severe than that of the critical efficacy trials.

Other secondary endpoints

Table 127 shows a summary of some secondary endpoint results as submitted. The results were not examined in detail. These analyses are presented on subjects with at least 1 diary card.

Table 127. Trial IA04: Secondary endpoints*

	Omalizumab n=191	**Control n=89**
Systemic corticosteroids		
No. (%) taking systemic corticosteroids	99 (51.8)	58 (65.2)
Days taking systemic corticosteroids; Median (min-max)	29.0 (1-368)	32.5 (1-370)
Unscheduled physician visits		
No. (%)	64 (33.5)	45 (50.6)
Days, Median (min-max)	2.0 (1-12)	3.0 (1-135)
Emergency room visits		
No. (%)	24 (12.6)	17 (19.1)
Days, Median (min-max)	1.0 (1-46)	2.0 (1-33)
Hospital stays		
No. (%)	16 (8.4)	8 (9.0)
Days, Median (min-max)	7.0 (1-53)	8.0 (1-21)
Absenteeism from work or school*		
No. (%)	83 (43.5)	51 (57.3)
Median (min-max), all social groups	14.0 (1-365)	28.0 (1-259)
Median (min-max) days , working group	7.5 (1-140)	10.0 (1-124)
Median (min-max) days, non-working group	41.0 (1-365)	106.5 (6-259)
Median (min-max) days, studying group	14.0 (2-118)	5.5 (3-11)

*Subjects with at least 1 diary card

FEV_1

Mean % predicted FEV_1 was balanced at baseline (means and standard deviation, omalizumab and control: 71.4 ± 21 (n=204) and 71.6 ± 22 (n=105), respectively) and changed very

little during the trial, with a very slight advantage of omalizumab (75.7 ± 21 (n=171) and 69.7 ± 22 (n=76), respectively). Interpretation of these data is complicated by dwindling numbers of subjects toward the end of the trial, but the mean differences were clinically not important.

Symptom scores and quality of life questionnaires

These results are not presented due to their inherent unreliability in an open-label trial.

Short-acting β-agonist-free days and puffs of β-agonist used

All data were submitted on the period following baseline (after treatment), and are not summarized here.

Use of inhaled corticosteroids

Table 128 shows use of inhaled corticosteroids as doses normalized to beclamethasone dipropionate. Mean dose of inhaled corticosteroid increased in control subjects, which is unexpected; use in omalizumab-treated subjects decreased. Interpretation of these data is complicated by dwindling numbers of subjects toward the end of the trial, with the potential for selection bias.

Table 128. Trial IA04: Daily doses of inhaled corticosteroid* at baseline and end of trial

		Omalizumab		Control
	n	Mean (SD)	n	Mean (SD)
At randomization	*206*	2219 (1519)	106	2097 (1433)
End of core period	*173*	1812 (1.22)	76	2214 (1558)
Difference	*173*	-342 (878)	76	68 (913)

*Beclomethasone dipropionate equivalents, μg

Concomitant medication use

There was no notable difference between the treatment groups in the proportions of subjects taking medications for asthma (reviewed by medication), other than summarized for corticosteroids.

Antibody

Antibody development to omalizumab was not assessed in this trial.

Summary: Trial IA04

Trial IA04 was an open-label trial comparing omalizumab to standard treatment in subjects with asthma of greater severity than enrolled in other trials reviewed in this submission. The trial's open-label design, the large number of dropouts early in the placebo group, and the retrospective assessment of the data on asthma exacerbations, make assessments of a treatment effect suggestive only. Given these profound limitations, the results on asthma exacerbations were consistent with those found in other trials in less severely affected asthmatic subjects. As in the other trials the effect on lung function as measured by FEV_1 was not notable.

ANTIGENICITY WITH SUBCUTANEOUS ADMINISTRATION

Because the marketed product is for subcutaneous administration, the results of the antibody determinations in trial Q0694g, where the product was administered intravenously, were not reviewed. Genentech tested followup samples from trials 008-011 (Table 129). Antibody determinations were not done in trials Q2143g or IA04.

Table 129. Subjects with antibody determinations at followup

Trial	omalizumab	placebo	(+) test
8	235	220	0
9	207	194	0
10	279	0*	1
11	118	119	0
Total	839	533	1

*Samples were obtained from 87 subjects who were switched from placebo to omalizumab during extension, prior to determination

Comment

The presence of only 1 positive sample makes a reliable determination of the effects of antibody on efficacy impossible.

GENENTECH'S INTEGRATED SUMMARIES OF CLINICAL DATA

Pooled analyses provided by Genentech were provided to address important issues concerning subpopulations that might derive more or less benefit from omalizumab, and to examine asthma-related clinical outcomes of importance.

Genentech pooled exacerbation data in trials 008-010. This was appropriate given the very similar data collection and the similarity of the subjects included. Rates for trial 011, the other blinded and well-controlled trial in the submission, were not pooled in the analysis as the definition of an exacerbation was different in that trial.

Exacerbation rate analyses

Analytical method for pooled exacerbation rate data

Genentech calculated the rate of protocol-defined asthma exacerbations in the stable steroid and steroid reduction phases of trials 008-010 in the following way:

- The asthma exacerbation rate was calculated as the number of events per subject, normalized by the number of weeks of exposure during a period, then adjusted for the actual period length. Rates were expressed per 100 subjects.
- Weeks at risk are computed as the difference between the subject's trial termination date and the date of first administration of trial agent.
- Analysis was done on all randomized subjects using the intent-to-treat principle. No imputation was performed for early discontinuation.

Table 130 and Table 131 shows the results of subgroup analyses, pooling data from trials 008-010, for the stable steroid and steroid reduction phases of the trials.

The following observations can be made:

- In children, the placebo rate was lower than the overall rate of exacerbation, and the omalizumab effect smaller, during the stable steroid phase. In the steroid reduction phase, the placebo rate was much higher, and there was more of a treatment effect.
- Small numbers of subjects in the geriatrics age group made a determination of effect problematic. The data showed a minimal treatment effect in the stable steroid phase, but some effect in the steroid reduction phase, associated with a higher placebo rate than in the overall population.
- Numbers of subjects in the geriatric subgroup were very small. There was little effect of omalizumab during the stable steroid phase, but during the steroid reduction period the placebo rate of exacerbations increased and a treatment effect was noted.
- Females appeared to experience more benefit than males in both periods, but the difference was more pronounced during the stable steroid phase.
- Rates of exacerbations were greater in subjects with a history of hospitalization, and the treatment effect was greater in these subjects than in those without such a history.
- In the subjects with less airflow obstruction (FEV_1 criterion) placebo rates were smaller compared to the overall population, and the treatment effect was smaller. Compared to the pooled analysis of just trials 008 and 009 (Table 151) the analysis that includes the pediatric trial shows more of a treatment effect in the higher FEV_1 subgroup. The reason for this is not clear.
- There is an apparent steroid dose-related treatment effect in the inhaled corticosteroid users, although the magnitude of the effects is unclear given that confidence interval on the difference between placebo and active treatment is very great at the high doses. This steroid dose trend is in contrast to the lack of treatment effect in trial 011's oral corticosteroid users and the small treatment effect in trial 011's inhaled steroid users. It is important to keep in mind that trial 011 contained a substantially larger population of subjects on high-dose inhaled corticosteroids.

Table 130. Pooled exacerbation rates* in stable steroid phases of trials 008-010 by subgroup

	Sample size		Exacerbations/total subject weeks at risk in period (Exacerbation rate)*		
	Omalizumab	Placebo	Omalizumab	Placebo	Rate Difference and 95% CI**
Overall Population	767	638	98/12391 (12.65)	161/10105 (25.49)	12.8 (7.8-18.0)
Age					
Children(<12 yrs.)	203	95	30/3294 (14.57)	21/1530 (21.96)	7.4 (-4.5-19.3)
Adolescents(>=12 to <18 yrs.)	60	52	6/959 (10.01)	12/796 (24.12)	14.1 (-3.4-31.6)
Adults(>=18 to <65 yrs.)	478	475	56/7714 (11.62)	124/7530 (26.35)	14.7 (8.6-20.9)
Geriatrics(>=65 yrs.)	26	16	6/424 (22.66)	4/248 (25.79)	3.1 (-31.3-37.5)
Gender					
Male	403	311	54/6472 (13.35)	60/4957 (19.36)	6.0 (-0.6-12.6)
Female	364	327	44/5919 (11.89)	101/5147 (31.40)	19.5 (11.8-27.2)
Race					
Caucasian	662	557	79/10740 (11.77)	137/8824 (24.84)	13.1 (7.7-18.4)
Non-Caucasian	105	81	19/1651 (18.41)	24/1280 (29.99)	11.6 (-4.3-27.5)
Hospitalization/emergency room visit in prior yr.					
Yes	128	98	25/2110 (18.96)	47/1602 (46.94)	28.0 (11.2-44.8)
No	639	540	73/10281 (11.36)	114/8502 (21.45)	10.1 (4.9-15.3)
Baseline FEV_1					
FEV_1 %Pred>=80%	274	193	30/4441 (10.81)	34/3123 (17.42)	6.6 (-1.1-14.3)
FEV_1 %Pred<80%)	493	445	68/7950 (13.69)	127/6982 (29.10)	15.4 (8.8-22.0)
Baseline inhaled steroid dose***					
Low	244	206	24/3944 (9.74)	35/3271 (17.12)	7.4 (-0.1-14.9)
Medium	493	400	67/7962 (13.46)	108/6323 (27.33)	13.9 (7.3-20.5)
High	30	32	7/486 (23.07)	18/510 (56.45)	33.4 (-0.5-67.3)

*Number of exacerbations/number of subjects, adjusted by the ratio between actual total subject weeks at risk and the nominal total weeks (i.e., for the stable steroid period: 16 weeks x 767 subjects=12272)---expressed per 100 subjects

**Placebo-omalizumab (expressed per 100 subjects)

*** Actuator dose: Trials 008 and 009, BDP dose (μg/day) ≥168 to <504 (low), ≥504 to ≤840 (medium), >840 (high); Trial 010 BDP dose (μg/day) ≥84 to <336 (low), ≥336 to ≤672 (medium), >672 (high)

Table 131. Pooled exacerbation rates* in steroid reduction phases of trials 008-010 by subgroup

	Sample size		Exacerbations/total subject weeks at risk in period (Exacerbation rate)*		
	Omalizumab	Placebo	Omalizumab	Placebo	Rate difference and 95% CI**
Overall Population	732	580	112/8896 (15.11)	151/7061 (25.66)	10.6 (5.2-15.9)
Age					
Children(<12 yrs.)	196	89	32/2376 (16.16)	34/1089 (37.48)	21.3 (6.5-36.2)
Adolescents(>=12 to <18 yrs.)	56	45	4/692 (6.94)	13/579 (26.96)	20.0 (2.6-37.4)
Adults(>=18 to <65 yrs.)	454	431	70/5514 (15.23)	97/5208 (22.35)	7.1 (1.0-13.3)
Geriatrics(>=65 yrs.)	26	15	6/314 (22.91)	7/186 (45.27)	22.4 (-18.8-63.6)
Male	378	289	57/4609 (14.84)	71/3513 (24.25)	9.4 (2.0-16.8)
Female	354	291	55/4287 (15.39)	80/3548 (27.06)	11.7 (3.9-19.5)
Race					
Caucasian	638	508	94/7793 (14.47)	130/6199 (25.17)	10.7 (5.0-16.3)
Non-Caucasian	94	72	18/1103 (19.59)	21/862 (29.22)	9.6 (-7.1-26.3)
Hospitalization/ER visit in prior yr.					
Yes	126	95	24/1543 (18.66)	50/1171 (51.24)	32.6 (15.3-50.0)
No	606	485	88/7353 (14.36)	101/5890 (20.58)	6.2 (0.8-11.6)
Baseline FEV_1					
FEV_1 %Pred>=80%	263	183	38/3188 (14.30)	33/2269 (17.45)	3.2 (-4.9-11.2)
FEV_1 %Pred<80%	469	397	74/5708 (15.56)	118/4792 (29.55)	14.0 (7.1-20.9)
Baseline inhaled steroid dose**					
Low	234	191	36/2854 (15.14)	41/2340 (21.02)	5.9 (-2.9-14.6)
Medium	469	360	72/5685 (15.20)	98/4370 (26.91)	11.7 (4.8-18.6)
High	29	29	4/357 (13.44)	12/351 (41.04)	27.6 (-1.1-56.4)

*Number of exacerbations/number of subjects, adjusted by the ratio between actual total subject weeks at risk and the nominal total weeks (i.e., for the stable reduction period: 12 weeks x 732 subjects=8784)---expressed per 100 subjects

**Placebo rate – omalizumab rate (expressed per 100 subjects)

** Actuator dose: Trials 008 and 009, BDP dose (μg/day) ≥168 to <504 (low), ≥504 to ≤840 (medium), >840 (high); Trial 010 BDP dose (μg/day) ≥84 to <336 (low), ≥336 to ≤672 (medium), >672 (high)

Analyses of asthma-related clinical outcomes

Genentech submits analyses for all controlled trials of several asthma-related clinical outcomes: hospitalizations, emergency room visits, intubations, and unscheduled medical care. Because unscheduled medical visits may have had relatively little impact on asthma medical care, this review will not summarize these results. There were no outpatient asthma-related intubations

reported for trials 008-010 (including the extension periods). There was no systematic collection of inpatient intubations for these trials, nor any collection of intubations during trials 011, IA04, or Q2143g.

Analytical method for hospitalizations and emergency room visits

The analysis was based on the intent-to-treat population, and included all randomized subjects. Rates were computed as the number while on a trial agent or under observation (open-label control) divided by total subjects-weeks at risk (days from first treatment or observation to termination date for a subject).

Hospitalizations

Table 132 shows Genentech's analysis of hospitalization rates.

Table 132. Rates* of hospitalizations in controlled trials

Trial (length)	Omalizumab-Treated Subjects	Control Subjects	Rate difference**	Rate Ratio and 95% CI
008C/E*** (52 Weeks)	1/13172 (0.39)	3/11928 (1.31)	0.9	0.30 (0.00, ∞)
009C/E (52 Weeks)	1/13670 (0.38)	10/12485 (4.16)	3.8	0.09 (0.00, 0.56)
010C/E (52 Weeks)	0/13691 (0.00)	5/2978 (8.73)	8.7	0.00 (Undefined)
011 (32 Weeks)	3/5485 (1.75)	0/5249 (0.00)	-1.75	∞ (Undefined)
IA04 (52 Weeks)	30/9489 (16.44)	14/4432 (16.43)	0	1.00 (0.35, 3.24)
Q2143g (24 Weeks)	31/28063 (2.65)	24/14381 (4.01)	1.4	0.66 (0.35, 1.28)
Overall****	66/83570 (4.11)	56/51452 (5.66)	1.6	0.73 (0.43, 1.21)

*Expressed for period length per 100 subjects. **** In the case of the overall rate, expressed for 52-week period per 100 subjects

**Calculated by CBER; control rate-omalizumab rate

***C/E=core and extension

Table 133 expresses the same data, but shows how many subjects experienced events.

Table 133. Incidence of hospitalization in controlled trials (% randomized)

Trial	Omalizumab	Control	Relative risk and 95% CI
008 Core + Extension	1/268 (0.4%)	2/257 (0.8%)	0.48 (0.04, 5.26)
009 Core + Extension	1/274 (0.4%)	8/272 (2.9%)	0.12 (0.02, 0.99)
010 Core	0/225 (0.0%)	5/109 (4.6%)	0.00 -
011 Core	1/176 (0.6%)	0/165 (0.0%)	-
IA04	15/205 (7.3%)	8/107 (7.5%)	0.98 (0.43, 2.23)
Q2143g	27/1262 (2.1%)	19/637 (3.0%)	0.72 (0.40, 1.28)
Overall 6 mos. studies	28/1663 (1.7%)	24/911 (2.6%)	0.64 (0.37, 1.10)
Overall 12 mos. studies	17/747 (2.3%)	18/636 (2.8%)	0.80 (0.42, 1.55)

Genentech calculated the durations of hospitalizations for trials 008-011. They were comparable (4.2 days for omalizumab and 5.4 days for control).

Comments

Numbers of subjects with hospitalizations in the trials was small, but the highest in trial IA04, predictable because of trial enrollment criteria. There was no benefit of omalizumab in open-label trial IA04, which enrolled possibly the refractory subjects.

Overall, omalizumab treatment was associated with a small drop in the rate of hospitalizations due to asthma. The overall treatment effect on the rate of hospitalization was small, amounting to a reduction of about 1.6 hospitalizations for every 100 subjects treated for a year.

Emergency room visits

Table 134 shows rates of emergency room visits calculated the same way as hospitalizations.

Table 134. Rates* of emergency room visits in controlled trials

Trial (length)	Omalizumab-Treated Subjects	Control Subjects	Rate Ratio	95% CI
008C/E (52 weeks)	3/13172 (1.18)	7/11928 (3.05)	0.39	(0.00,1.76)
009C/E (52 weeks)	3/13670 (1.14)	7/12485 (2.92)	0.39	(0.00, 2.75)
010C/E (52 weeks)	8/13691 (3.04)	6/2978 (10.48)	0.29	(0.09, 1.07)
011 (32 weeks)	0/5485 (0.00)	4/5249 (2.44)	0.00	Undefined
IA04 (52 weeks)	31/9489 (16.99)	35/4432 (41.06)	0.41	(0.18, 1.00)
Q2143g (24 weeks)	46/28063 (3.93)	28/14381 (4.67)	0.84	(0.46, 1.65)
Overall***	91/83570 (5.66)	87/51452 (8.79)	0.64	(0.42, 1.00)

*Expressed for period length per 100 subjects or ***for 52-week period per 100 subjects
** C/E=core and extension

Table 135 expresses the same data, but shows how many subjects experienced events.

Table 135. Incidence of emergency room visit for asthma in controlled trials

Trial	Omalizumab	Control	Relative Risk and 95% CI
008 Core + Extension	3/268 (1.1%)	7/257 (2.7%)	0.41 (0.11, 1.57)
009 Core + Extension	3/274 (1.1%)	5/272 (1.8%)	0.60 (0.14, 2.47)
010 Core	4/225 (1.8%)	6/109 (5.5%)	0.32 (0.09,1.12
011 Core	0/176 (0.0%)	4/165 (2.4%)	0.00 -
IA04 (5)	19/205 (9.3%)	15/107 (14.0%)	0.66 (0.35, 1.25)
Q2143g	35/1262 (2.8%)	21/637 (3.3%)	0.84 (0.49, 1.43)
Overall 6 mos. studies	39/1663 (2.3%)	31/911 (3.4%)	0.69 (0.43, 1.10)
Overall 12 mos. studies	25/747 (3.3%)	27/636 (4.2%)	0.79 (0.46, 1.34)

Comments

Overall, omalizumab treatment was associated with a small drop in the rate of emergency room visits due to asthma. The overall treatment effect on the rate of emergency room visits was small, amounting to a reduction of about 3 for every 100 subjects treated for a year.

Classification of subjects enrolled in trials 008-010

As discussed in the background section of this document, the NHLBI 1997 Guidelines provide a means to classify and label patients with asthma according to clinical features and measurements. Genentech submitted analyses of the subjects in trials 008-010 according to interpretations of these Guidelines. Review of these analyses helps to put the clinical trial data into perspective.

Genentech summarizes the classification of the asthma subjects enrolled in the controlled clinical trials 008-011. Baseline characteristics were used to determine classification of subjects.

Subjects were classified into the most severe category by qualities prior to randomization (from diary cards for the previous 14 days) according to the following rules (Table 136):

Table 136. NHLBI and clinical trial criteria for classifying asthma severity in Genentech trials

Clinical Feature	NHLBI Guideline Criteria	Omalizumab Clinical Trial Criteria
Severe persistent features		
Pulmonary function	FEV_1 or PEF ≤60% predicted	FEV_1 ≤60% predicted
Nocturnal symptoms	"Frequent"	≥7 times in 14 days
Physical activity limitations	"Physical activity limited"	Reported "symptoms that caused discomfort, at times limiting strenuous activity" (or greater) for ≥7 of 14 days
Moderate persistent features		
Pulmonary function	FEV_1 or PEF >60% to <80% predicted	FEV_1 >60% to <80% predicted
Nocturnal symptoms	>1 time per week	3–6 times in 14 days
β_2 agonist use	Daily use of inhaled short-acting β_2 agonist	≥1 puff per day of albuterol for ≥10 of 14 days
Mild persistent/intermittent features		
Pulmonary function	FEV_1 or PEF ≥80% predicted	FEV_1 ≥80% predicted
Nocturnal symptoms	0 to >2 times per month	0–4 times per month
β_2 agonist use	Less than daily use of inhaled short-acting β_2 agonist	<10 of 14 days with ≥1 puff per day of albuterol

Subjects were assessed for the most severe category first; if they failed to qualify, they were assessed for the next lower level of severity. Subjects not meeting criteria for severe or moderately persistent asthma were classified as having mild persistent or mild intermittent asthma. Subjects with missing values were classified using only the criteria with non-missing values.

The results of Genentech's classification are shown in Table 137. In the critical efficacy trials, the great majority of subjects were classified as severe persistent. However, trial 011 enrolled only a little less than 1/2 of the subjects who were classified as severe persistent. This may have been a function of the fact that the great majority of them were on "high" doses of corticosteroids (Table 138).

The plurality of subjects in the trials 008 and 009 (about 40%) qualified on the basis of having "frequent" nocturnal symptoms in combination with "limited physical activity."

Table 137. Subject baseline asthma severity in trials 008-011

NHLBI Severity and Criteria[a]	Study 008 (n=525)	Study 009 (n=546)	Study 010 (n=334)	Study 011 (n=341)
Severe persistent	522 (99%)	511 (94%)	69 (21%)	160 (47%)
FEV_1 ≤60% predicted only	2 (<1%)	1 (<1%)	13 (4%)	51 (15%)
Frequent nocturnal symptoms only	27 (5%)	73 (13%)	31 (9%)	26 (8%)
Limited physical activity only	131 (25%)	80 (15%)	10 (3%)	26 (8%)
FEV_1 ≤60% predicted AND Frequent nocturnal symptoms	7 (1%)	21 (4%)	0 (0%)	12 (4%)
FEV_1 ≤60% predicted AND Limited physical activity	48 (9%)	25 (5%)	2 (<1%)	18 (5%)
Frequent nocturnal symptoms AND Limited physical activity	209 (40%)	222 (41%)	13 (4%)	14 (4%)
FEV_1 ≤60% predicted AND Frequent nocturnal symptoms AND Limited physical activity	98 (19%)	89 (16%)	0 (0%)	13 (4%)
Moderate persistent	2 (<1%)	25 (5%)	148 (44%)	115 (34%)
FEV_1 >60% and <80% predicted only	0 (0%)	8 (2%)	61 (18%)	51 (15%)
Nocturnal symptoms >1 time/wk only	1 (<1%)	3 (<1%)	21 (6%)	7 (2%)
Daily-use inhaled β_2-agonist only	0 (0%)	2 (<1%)	25 (8%)	14 (4%)
FEV_1 >60% and <80% predicted AND Nocturnal symptoms >1 time/wk	0 (0%)	0 (0%)	12 (4%)	13 (4%)
FEV_1 >60% and <80% predicted AND Daily-use inhaled β_2-agonist	1 (<1%)	10 (2%)	17 (5%)	21 (6%)
Nocturnal symptoms >1 time/wk AND Daily-use inhaled β_2-agonist	0 (0%)	0 (0%)	8 (2%)	3 (<1%)
FEV_1 >60% and <80% predicted AND Nocturnal symptoms >1 time/wk AND Daily-use inhaled β_2-agonist	0 (0%)	2 (<1%)	4 (1%)	6 (2%)
Mild persistent/intermittent	1 (<1%)	10 (2%)	117 (35%)	66 (19%)

Genentech also classified baseline inhaled corticosteroid use by trial (Table 138).

Table 138. Baseline inhaled corticosteroid dose classification in trials 008-010

Dose Group[a]	Study 008 (n=525)	Study 009 (n=546)	Study 010 (n=334)	Study 011 (n=341)
Low	158 (30%)	122 (22%)	170 (51%)	0 (0%)
Medium	365 (70%)	364 (67%)	164 (49%)	4 (1%)
High	2 (<1%)	60 (11%)	0 (0%)	337 (99%)

[a] Defined per NHLBI guidelines: Studies 008 and 009, adult BDP dose (µg/day) ≥168 to <504 (low), ≥504 to ≤840 (medium), >840 (high); Study 010, child BDP dose (µg/day) ≥84 to <336 (low), ≥336 to ≥672 (medium), >672 (high); Study 011, adult fluticasone dose (mcg/day) ≥88 to <264 (low), ≥264 to ≤660 (medium), >660 (high). All dosages expressed as the actuator dose.

The majority of subjects in the critical efficacy trials were on medium doses of corticosteroids at baseline; the great majority of subjects in trial 011 were on high doses of inhaled corticosteroids. This is consistent with the design of the trials.

Comments

The data show that the great majority of subjects in the critical efficacy trials would have been classified into the severe persistent category. Nevertheless, as stated in the introduction, subjects with the highest degrees of refractoriness (need for oral corticosteroids or histories of hospitalizations) were mostly not studied in an adequate and well-controlled trial. In fact, evidence from trial 011 suggests that omalizumab does not confer a benefit in subjects taking oral corticosteroids.

FINANCIAL CONFLICTS OF INTEREST DISCLOSURE

Genentech and Novartis sent letters detailing financial information to disclose to the investigators in the critical efficacy trials (Table 139). Although not all subinvestigators responded, nearly all principal investigators did.

Table 139. Financial disclosure data completion and results

Trial	Proportion of investigators with responses	Proportion of principal investigators with responses*	Responders with conflict
008	89%	100	0
009	89%	100*	0*
010	86%	96%**	0**

*One principal investigator who was not available at the site had been replaced with an investigator who reported no conflict

**One principal investigator, whose site enrolled 10 subjects, did not respond

Comments

The great majority of investigators responded with a statement of no conflict of interest, including nearly all the principal investigators. The disclosure statements do not point to significant financial conflicts of interest.

FOREIGN AND POST-MARKETING EXPERIENCE

Omalizumab has not been marketed anywhere to date.

SUMMARY OF EFFICACY

- Trial Q0694g, a dose-finding trial of omalizumab given by the intravenous route and that used a production method that was later changed, provided results consistent with those of the critical trials to follow. Omalizumab was associated with lower asthma exacerbation rates; however, difference in changes in symptom scores were small, and equivocal differences were seen in measures of pulmonary function.
- The critical efficacy trials were designed to capture relevant clinical endpoints. These trials were adequately conducted to enable a determination of efficacy. These trials showed:

- Omalizumab treatment was associated with a reduction in exacerbations in subjects whose asthma was managed with moderate-to-high doses of inhaled corticosteroids through the adult and pediatric trials. In trials 008 and 009 core periods, the percentages of subjects with at least 1 exacerbation were decreased by 7-13% in the stable steroid phases, and 5-7% in the steroid reduction phases. Mean observed exacerbations per subject were reduced by 0.10 to 0.18 (range between trials) in the stable steroid period and 0.07 to 0.08 in the steroid reduction period. While statistically significant, the effect size in absolute terms was small, and was seen in a minority of subjects in the trials, as the large majority of placebo subjects had no exacerbations in any trial. These effects were robust to data imputation sensitivity analyses.
- The omalizumab-associated reduction in exacerbations occurred among the inhaled corticosteroid-managed subjects in most subgroups of disease severity (within the ranges of severity studied in the trials), numbers of allergens, IgE level, age, and weight. However, there was more benefit in females than in males, and there was little benefit in subjects with the lowest degrees of airflow obstruction ($FEV_1 \geq 80\%$ predicted).
- The effects of omalizumab on exacerbation rate reduction in inhaled corticosteroid-managed subjects persisted for the time of observation (a year) during treatment.
- Omalizumab treatment allowed a larger proportion of inhaled corticosteroid-managed subjects in treated groups than in placebo groups to lower or discontinue inhaled corticosteroid treatment. In these trials the percents of subjects in omalizumab with complete cessation of inhaled corticosteroid was 40-44%; that of placebo, 19%. The steroid reduction effect was seen, by design, after several months of treatment with omalizumab. The benefit of discontinuation from inhaled corticosteroid treatment would be expected to be relatively minor compared to a discontinuation from oral corticosteroids, since the intensity of systemic exposure in inhaled corticosteroid use is much less.
- Measures of treatment effect other than exacerbation rates or steroid use provided small support for the effects of omalizumab in inhaled corticosteroid-managed subjects:
  - Asthma symptom score data were consistent with a small benefit of omalizumab.
  - Rescue medication use was lowered by a clinically unimportant amounts in omalizumab-treated subjects.
  - Data on lung physiology (volumes and flow) provide support, although weak, for the primary clinical endpoints of exacerbation reduction and reduction of steroid use. In all trials, differences between omalizumab-treated and placebo subjects generally were clinically inconsequential.
  - Rates of emergency room visits and hospitalizations were small. The reduction in rates was small as well.

- Trial 010 was an adequate and well-controlled pediatric trial that provided support for the results in the critical efficacy trials. It showed a treatment effect on corticosteroid reductions (55% of omalizumab-treated subjects were able to discontinue inhaled corticosteroids entirely as compared to 39% of placebo-treated subjects). The treatment effect on exacerbations was of the same or greater magnitude compared to that seen in trials 008 and 009 (percents of subjects with at least 1 exacerbation were reduced by 6% in the stable steroid phase and 16% in the steroid reduction phase). Efficacy was impossible to establish in the extension period of this trial as all subjects received omalizumab.
- Trial 011 was an adequate and well-controlled trial in asthmatic subjects on high doses of inhaled corticosteroid and in subjects on oral corticosteroids. This trial showed:
  - Subjects on high inhaled doses of corticosteroid treated with omalizumab were more able to eliminate inhaled corticosteroid use compared to subjects in the placebo

group, but the proportion of these subjects was not as great as seen in the critical efficacy trials (21% of omalizumab-treated subjects and 15% of placebo-treated subjects).
    - Treatment with omalizumab was not associated with an increased ability to reduce oral corticosteroid use.
    - Exacerbation rates were decreased among inhaled corticosteroid users, only in the steroid reduction phase. This is in contrast to the results in the critical efficacy trials, in subjects on moderate inhaled corticosteroid doses, where a treatment effect was seen in both the stable steroid and steroid reduction phases. The subgroup analyses of trials 008-010 suggest that efficacy in reducing exacerbation rates was maintained in the high dose groups in these trials. However, the lack of effect in trial 011, in which a larger group of subjects generally received high doses of inhaled corticosteroids is concerning, especially given the lack of benefit in oral corticosteroid users.
    - Intertreatment differences in symptom scores and lung physiology were minimal, as in the critical efficacy trials.
    - In sum, the results of trial 011 suggest that omalizumab would not be of benefit to oral corticosteroids users, and that its benefit for high-dose inhaled corticosteroid users is not as great as its benefit in moderate dose inhaled corticosteroid users.
- Trial Q2143g did not restrict concomitant medication use upon enrollment, thus it would be expected that the subjects would be less easily managed than those in the critical efficacy trials. Its results in exacerbation rates were consistent with those in the critical efficacy trials. Like in the critical efficacy trials, there was minimal effect on pulmonary function. Because of the open-label nature of the trial, these results are suggestive only.
- Trial IA04 enrolled subjects with histories of more refractory asthma than in the critical efficacy trials. The analysis of this trial was hampered by large numbers of dropouts, the retrospective nature of the analysis of exacerbations, and the open-label nature of the trial. Given these marked limitations, the results on exacerbation rates and minimal effects on pulmonary function were consistent with those of the other important trials reviewed here.
- Data in the clinical trials are restricted primarily to subjects with known skin test sensitivity. Inadequate information is available to determine the effects of omalizumab on subjects without skin test sensitivity to common allergens.
- Numbers of geriatric subjects were very small, and determination of treatment effects problematic. There are no efficacy data to create a special concern for the geriatric population.

RECOMMENDATION

This marketing application has shown that omalizumab has efficacy in reducing asthma exacerbations in a subpopulation of adults and adolescents with asthma. Based on this demonstration of efficacy, and the safety profile of omalizumab, I recommend that omalizumab be approved for these patients. Deficiencies in the data, concerning efficacy in patients on oral corticosteroids or with FEV_1 percent predicted ≥80%, may be addressed in postmarketing trials.

REFERENCES

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2. Global strategy for asthma management and prevention, National Institutes of Health National Heart, Lung, and Blood Institute, Global Initiative for Asthma (GINA) 2002 revision.
3. Surveillance for Asthma--United States, 1980-1999. Morbidity and Mortality Weekly Report, March 29, 2002, volume 51, number SS-1.

APPENDIX

1. CBER subgroup analyses of trials 008 and 009

Table 140. Trial 008: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

Subgroup			Stable steroid phase		Steroid reduction phase	
			Omalizumab	Placebo	Omalizumab	Placebo
Ethnicity	White	*n*	*238*	*229*	*238*	*229*
		0	212 (89)	190 (83)	203 (85)	185 (81)
		≥1	26 (11)	39 (17)	35 (15)	44 (19)
	Black	*n*	*21*	*16*	*21*	*16*
		0	17 (81)	9 (56)	18 (86)	10 (63)
		≥1	4 (19)	7 (44)	3 (14)	6 (38)
	Oriental	*n*	*1*	*3*	*1*	*3*
		0	1	3	1	3
		≥1	0	0	0	0
	Other	*n*	*8*	*9*	*8*	*9*
		0	8	8	7	8
		≥1	0	1	1	1
Combined severity measures	$FEV_1 \leq 65\%$ and total symptom score >4	*n*	*58*	*53*	*58*	*53*
		0	48 (83)	37 (70)	51 (88)	35 (66)
		≥1	10 (17)	16 (30)	7 (12)	18 (34)
	Others	*n*	*210*	*204*	*210*	*204*
		0	190 (90)	173 (85)	178 (85)	171 (84)
		≥1	20 (10)	31 (15)	32 (15)	33 (16)
Sex	Male	*n*	*104*	*111*	*104*	*111*
		0	93 (89)	93 (84)	91 (88)	85 (77)
		≥1	11 (11)	18 (16)	13 (13)	26 (23)
	Female	*n*	*164*	*146*	*164*	*146*
		0	145 (88)	117 (80)	138 (84)	121 (83
		≥1	19 (12)	29 (20)	26 (16)	25 (17)
Age	12-17	*n*	*20*	*21*	*20*	*21*
		0	19 (95)	16 (76)	19 (95)	13 (62)
		≥1	1 (5)	5 (24)	1 (5)	8 (38)
	18-64	*n*	*241*	*229*	*241*	*229*
		0	213 (88)	189 (83)	205 (85)	188 (82)
		≥1	28 (12)	40 (17)	36 (15)	41 (18)
	65	*n*	*7*	*7*	*7*	*7*
		0	6 (86)	5 (71)	5 (71)	5 (71)
		≥1	1 (14)	2 (29)	2 (29)	2 (29)

Table 141. Trial 009: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

Subgroup			Stable steroid phase		Steroid reduction phase	
			Omalizumab	Placebo	Omalizumab	Placebo
Ethnicity	White	*n*	*256*	*242*	*256*	*242*
		0	231 (90)	184 (76)	231 (90)	202 (83)
		≥1	25 (10)	58 (24)	25 (10)	40 (17)
	Black	*n*	*11*	*11*	*11*	*11*
		0	10 (91)	9 (82)	10 (91)	9 (82)
		≥1	1 (9)	2 (18)	1 (9)	2 (18)
	Oriental	*n*	*2*	*6*	*2*	*6*
		0	1	6	2	6
		≥1	1	0	0	0
	Other	*n*	*5*	*13*	*5*	*13*
		0	5	10	5	11
		≥1	0	3	0	2
Combined severity measures	$FEV_1 \leq 65\%$ and total symptom score >4	*n*	*60*	*59*	*60*	*59*
		0	48 (80)	38 (64)	54 (90)	47 (80)
		≥1	12 (20)	21 (36)	6 (10)	12 (20)
	Others	*n*	*214*	*213*	*214*	*213*
		0	199 (93)	171 (80)	194 (91)	181 (85)
		≥1	15 (7)	42 (20)	20 (9)	32 (15)
Sex	Male	*n*	*141*	*127*	*141*	*127*
		0	128 (91)	102 (80)	131 (93)	114 (90)
		≥1	13 (9)	25 (20)	10 (7)	13 (10)
	Female	*n*	*133*	*145*	*133*	*145*
		0	119 (89)	107 (74)	117 (88)	114 (79)
		≥1	14 (11)	38 (26)	16 (12)	31 (21)
Age	12-17	*n*	*18*	*17*	*18*	*17*
		0	16 (89)	16 (94)	18 (100)	16 (94)
		≥1	2 (11)	1 (6)	0	1 (6)
	18-64	*n*	*237*	*246*	*237*	*246*
		0	217 (92)	185 (75)	214 (90)	206 (84)
		≥1	20 (8)	61 (25)	23 (10)	40 (16)
	65	*n*	*19*	*9*	*19*	*9*
		0	14 (74)	8 (89)	16 (84)	6 (67)
		≥1	5 (26)	1 (11)	3 (16)	3 (33)

Table 142. Trial 008: Age: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

Subgroup			Stable steroid phase		Steroid reduction phase	
			Omalizumab	Placebo	Omalizumab	Placebo
Age	≤31	*n*	*66*	*77*	*66*	*77*
		0	56 (85)	64 (83)	60 (91)	61 (79)
		≥1	10 (15)	13 (17)	6 (9)	16 (21)
	32-≤40	*n*	*67*	*54*	*67*	*54*
		0	59 (88)	44 (81)	58 (87)	45 (83)
		≥1	8 (12)	10 (19)	9 (13)	9 (17)
	41-≤48	*n*	*82*	*60*	*82*	*60*
		0	77 (94)	46 (77)	73 (89)	48 (80)
		≥1	5 (6)	14 (23)	9 (11)	12 (20)
	≥49	*n*	53	66	53	66
		0	46 (87)	56 (85)	38 (72)	52 (79)
		≥1	7 (13)	10(15)	15 (28)	14 (21)

Table 143. Trial 009: Age: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

Subgroup			Stable steroid phase		Steroid reduction phase	
			Omalizumab	Placebo	Omalizumab	Placebo
Age	≤29	*n*	*70*	*75*	*70*	*75*
		0	63 (90)	61 (81)	67 (96)	64 (85)
		≥1	7 (10)	14 (19)	3 (4)	11 (15)
	30-≤39	*n*	*75*	*63*	*75*	*63*
		0	71 (95)	51 (81)	71 (95)	54 (86)
		≥1	4 (5)	12 (19)	4 (5)	9 (14)
	40-≤50	*n*	*58*	*73*	*58*	*73*
		0	54 (93)	51 (70)	48 (83)	61 (84)
		≥1	4 (7)	22 (30)	10 (17)	12 (16)
	≥51	*n*	*71*	*61*	*71*	*61*
		0	59 (83)	46 (75)	62 (87)	49 (80)
		≥1	12 (17)	15 (25)	9 (13)	12 (20)

Table 144. Trials 008 and 009: Allergen sensitivities: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		TRIAL 008				TRIAL 009			
		Stable steroid		Steroid reduction		Stable steroid		Steroid reduction	
# Allergens		Omlzmb	Placebo	Omlzmb	Placebo	Omlzmb	Placebo	Omlzmb	Placebo
0	*n*	*1*	*1*	*1*	*1*	*0*	*1*	*0*	*1*
	%≥1	0	0	0	0	-	0	-	0
1	*n*	*22*	*16*	*22*	*16*	*65*	*71*	*65*	*71*
	%≥1	0	19	0	31	14	24	6	20
2	*n*	*52*	*52*	*52*	*52*	*94*	*98*	*94*	*98*
	%≥1	13	21	15	17	10	18	10	12
3	*n*	*70*	*73*	*70*	*73*	*115*	*102*	*115*	*102*
	%≥1	11	21	13	16	8	27	11	18
4	*n*	*76*	*75*	*76*	*75*	-	-	-	-
	%≥1	11	13	17	20	-	-	-	-
5	*n*	*47*	*40*	*47*	*40*	-	-	-	-
	%≥1	15	20	19	25	-	-	-	-
	total	*268*	*257*	*268*	*257*	*274*	*272*	*274*	*272*

Table 145. Trials 008 and 009: Baseline BDP dose: Subjects (proportions of group) with 0 or any number of exacerbations---observed exacerbations

		TRIAL 008					TRIAL 009			
		Stable steroid		Steroid reduction			Stable steroid		Steroid reduction	
BDP dose (μg/day)		Omlzmb	Placebo	Omlzmb	Placebo	BDP dose (μg/day)	Omlzmb	Placebo	Omlzmb	Placebo
420	*n*	*77*	*80*	*77*	*80*	500	*59*	*55*	*59*	*55*
	% ≥1	8	10	17	19		7	18	10	11
504	*n*	*89*	*74*	*89*	*74*	600	*73*	*67*	*73*	*67*
	% ≥1	10	15	15	19		4	15	5	6
588	*n*	*4*	*4*	*4*	*4*	800	*50*	*47*	*50*	*47*
	% ≥1	0	25	0	0		2	32	16	13
672	*n*	*57*	*58*	*57*	*58*	800	*60*	*57*	*60*	*57*
	% ≥1	11	19	11	19		18	28	10	33
840	*n*	*39*	*37*	*39*	*37*	1000	*27*	*28*	*27*	*28*
	% ≥1	23	38	15	24		26	32	7	29
	total	*262*	*251*	*262*	*251*		*269*	*254*	*269*	*254*

Table 146. Trials 008 and 009: Baseline % FEV_1: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		TRIAL 008				TRIAL 009				
		Stable steroid		Steroid reduction			Stable steroid		Steroid reduction	
% FEV_1 Quartile		Omlzmb	Placebo	Omlzmb	Placebo	% FEV_1 Quartile	Omlzmb	Placebo	Omlzmb	Placebo
≤58%	*n*	*67*	*68*	*67*	*68*	≤61%	*74*	*73*	*74*	*73*
	% ≥1	12	28	16	31		19	32	8	19
58.01 to ≤69.0	*n*	*70*	*75*	*70*	*75*	>61 to ≤71.0	*71*	*67*	*71*	*67*
	% ≥1	10	17	13	23		6	30	11	22
69.01 to ≤78.0	*n*	*57*	*59*	*57*	*59*	>71 to ≤80.0	*59*	*68*	*59*	*68*
	% ≥1	11	19	11	12		8	12	8	15
>78.01	*n*	*74*	*55*	*74*	*55*	>80	*70*	*64*	*70*	*64*
	% ≥1	12	7	18	11		6	19	10	8
	total	*268*	*257*	*268*	*257*	*total*	*274*	*272*	*274*	*272*

Table 147. Trials 008 and 009: Baseline IgE: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		TRIAL 008					TRIAL 009			
		Stable steroid		Steroid reduction			Stable steroid		Steroid reduction	
IgE quartile (IU/ml)		Omlzmb	Placebo	Omlzmb	Placebo	IgE quartile (IU/ml)	Omlzmb	Placebo	Omlzmb	Placebo
≤70	*n*	*70*	*63*	*70*	*63*	≤86	*65*	*74*	*65*	*74*
	% ≥1	11	29	20	17		15	28	17	14
71 to ≤142	*n*	*71*	*61*	*71*	*61*	87 to ≤167	*66*	*68*	*66*	*68*
	% ≥1	10	11	15	16		8	13	9	16
143 to ≤244	*n*	*67*	*62*	*67*	*62*	168 to ≤305	*70*	*68*	*70*	*68*
	% ≥1	9	13	7	23		7	28	7	21
>245	*n*	*60*	*71*	*60*	*71*	>306	*73*	*62*	*73*	*62*
	% ≥1	13	20	15	23		10	23	5	15
	total	*268*	*257*	*268*	*257*	*total*	274	272	274	272

Table 148. Trials 008 and 009: Weight: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		TRIAL 008					TRIAL 009			
		Stable steroid		Steroid reduction			Stable steroid		Steroid reduction	
Weight Quartile (kg)		Omlzmb	Placebo	Omlzmb	Placebo	Weight Quartile (kg)	Omlzmb	Placebo	Omlzmb	Placebo
≤65	*n*	*66*	*67*	*66*	*67*	≤65	*75*	*72*	*75*	*72*
	% ≥1	8	19	12	18		13	25	11	22
66 to ≤77	*n*	*69*	*66*	*69*	*66*	66 to ≤76	*70*	*65*	*70*	*65*
	% ≥1	13	11	10	20		11	22	9	14
78 to ≤91	*n*	*63*	*58*	*63*	*58*	77 to ≤88	*64*	*71*	*64*	*71*
	% ≥1	10	19	24	14		6	21	8	20
>92	*n*	*70*	*66*	*70*	*66*	>89	*65*	*64*	*65*	*64*
	% ≥1	14	24	13	27		8	25	11	8
	total	*268*	*257*	*268*	*257*	*total*	*274*	*272*	*274*	*272*

Table 149. Trials 008 and 009: Total Symptom Score: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		TRIAL 008					TRIAL 009			
		Stable steroid		Steroid reduction			Stable steroid		Steroid reduction	
Total symptom score		Omlzmb	Placebo	Omlzmb	Placebo	Total symptom score	Omlzmb	Placebo	Omlzmb	Placebo
≤3.3571	*n*	*62*	*68*	*62*	*68*	≤3.1429	*77*	*60*	*77*	*60*
	% ≥1	6	13	15	22		8	15	5	8
3.3572 to ≤4.0	*n*	*71*	*66*	*71*	*66*	3.1430 to ≤3.9286	*62*	*71*	*62*	*71*
	% ≥1	13	14	17	17		8	17	8	17
4.001 to ≤4.9231	*n*	*61*	*63*	*61*	*63*	3.9287 to ≤4.8571	*69*	*59*	*69*	*59*
	% ≥1	5	19	8	22		10	32	10	20
>4.9231	*n*	*73*	*60*	*73*	*60*	>4.8572	*64*	*77*	*64*	*77*
	% ≥1	19	28	18	18		14	29	16	18
	total	*267*	*257*	*267*	*257*	*total*	272	267	272	267

Table 150. Trials 008 and 009:Doctor Visits (prior to trial): Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		TRIAL 008				TRIAL 009			
		Stable steroid		Steroid reduction		Stable steroid		Steroid reduction	
Doctor visits		Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo
≤1	*n*	*225*	*209*	*225*	*209*	*211*	*206*	*211*	*206*
	% ≥1	11	15	14	17	9	19	9	14
≥2	*n*	*43*	*48*	*43*	*48*	*63*	*66*	*63*	*66*
	% ≥1	14	33	16	31	14	36	13	23
	total	268	257	268	257	274	272	274	272

Table 151. Trials 008 and 009: Genentech's analysis by FEV_1 category*

Study/ Study Period (Length)	Baseline FEV_1 % Predicted	Sample Size (Omalizumab/ Placebo)	Omalizumab-Treated Subjects	Placebo-Treated Subjects	Rate difference	Rate Ratio (95% CI) *p-value*
Trial 008						
Stabilization (16 wk)	≥80%	61/49	11/1000 (17.60)	5/797 (10.04)	-7.6	1.75 (0.56, 6.61) *p=0.36*
	<80%	207/208	25/3317 (12.06)	54/3249 (26.59)	14.5	0.45 (0.26, 0.76) *p<0.01*
Steroid Redn (12 wk)	≥80%	60/47	14/715 (23.51)	5/571 (10.50)	-13.0	2.24 (0.83, 7.29) *p=0.14*
	<80%	195/187	30/2360 (15.26)	55/2247 (29.37)	14.1	0.52 (0.32, 0.82) *p<0.01*
Trial 009						
Stabilization (16 wk)	≥80%	76/72	4/1231 (5.20)	13/1170 (17.77)	12.6	0.29 (0.08, 0.86) *p=0.04*
	<80%	198/200	25/3209 (12.47)	65/3147 (33.05)	20.6	0.38 (0.23, 0.60) *p<0.01*
Steroid Redn (12 wk)	≥80%	72/67	7/874 (9.61)	5/828 (7.24)	-2.4	1.33 (0.38, 5.00) *p=0.65*
	<80%	189/178	26/2336 (13.35)	49/2161 (27.20)	13.9	0.49 (0.29, 0.81) *p<0.01*
Trials 008 and 009 pooled						
Stabilization (16 wk)	≥80%	137/121	15/2231 (10.76)	18/1967 (14.64)	3.9	0.73 (0.34, 1.56) *p=0.42*
	<80%	405/408	50/6525 (12.26)	119/6396 (29.77)	17.5	0.41 (0.28, 0.59) *p<0.01*
Steroid Redn (12 wk)	≥80%	132/114	21/1588 (15.86)	10/1400 (8.57)	-7.3	1.85 (0.85, 4.34) *p=0.13*
	<80%	384/365	56/4696 (14.31)	104/4409 (28.31)	14.0	0.51 (0.36, 0.71) *p<0.01*

Method:

- The asthma exacerbation rate was estimated as the total number of exacerbations during a period divided by the total subject-weeks at risk. Weeks at risk are computed as the difference between the subject's trial termination date and the date of first administration of trial agent.
- Analysis was done on all randomized subjects using the intent-to-treat principle. No imputation was performed for early discontinuation.
- Rates are expressed as numbers of exacerbations/ total subject weeks at risk (per 100 subjects).

Table 152. Trials 008 and 009: Morning, nocturnal, and daytime asthma symptom scores

			Baseline		End stable phase		End steroid reduction	
			Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo
Trial 008	Morning	*n*	*268*	*257*	*256*	*239*	*243*	*222*
		mean	0.82	0.79	0.51	0.59	0.5	0.58
		median	1	0.93	0.5	0.63	0.5	0.69
	Nocturnal	*n*	*268*	*257*	*256*	*239*	*243*	*222*
		mean	1.18	1.14	0.6	0.73	0.5	0.67
		median	1.14	1	0.22	0.54	0.13	0.4
	Daytime	*n*	267	257	256	238	244	222
		mean	2.29	2.3	1.35	1.59	1.28	1.53
		median	2.23	2.29	1.31	1.45	1.16	1.5
Trial 009	Morning	*n*	*273*	*269*	*263*	*247*	*248*	*229*
		mean	0.77	0.75	0.52	0.56	0.52	0.56
		median	0.93	0.93	0.44	0.61	0.5	0.57
	Nocturnal	*n*	*273*	*269*	*263*	*248*	*251*	*230*
		mean	1.18	1.29	0.66	0.95	0.57	0.83
		median	1.14	1.29	0.36	0.83	0.23	0.7
	Daytime	*n*	272	268	264	248	250	229
		mean	1.99	2.01	1.34	1.53	1.26	1.42
		median	2	2	1.27	1.51	1.13	1.24

Table 153. Trials 008 and 009: Proportions of subjects with any degree of worsening or an improvement from core period baseline of ³ 0.5 points in the Juniper asthma quality of life questionnaire at the end of the extension period

	Trial 008		Trial 009	
	Omlzmb *N=234*	Placebo *N=212*	Omlzmb *N**	Placebo *N=157*
Activities				
Worsening (<0)	15%	26%	19%	23%
≥0.5 better	69%	59%	61%	57%
Emotions				
Worsening (<0)	18%	19%	13%	20%
≥0.5 better	69%	59%	61%	54%
Symptoms				
Worsening (<0)	9%	16%	13%	11%
≥0.5 better	79%	67%	73%	70%
Exposure				
Worsening (<0)	16%	25%	21%	15%
≥0.5 better	72%	61%	65%	65%

*n=184-185

While the protocol for the questionnaire specifies that 5 individual activities should be scored, a lack of instruction on this item made the interpretation of these items problematic. The data shown are data without the 5 specified activities.

Trial 010

Tabulations of observed exacerbations during the stable steroid and steroid reduction phases.

Table 154. Trial 010: Asthma exacerbations in stable steroid phase, observed (subjects, %)*

	Q2w		Q4w		Overall	
Number of exacerbations	Omlzmb n=76	Placebo n=35	Omlzmb n=149	Placebo n=74	Omlzmb n=225	Placebo n=109
0	64 *84%*	29 *83%*	133 *89%*	60 *81%*	197 *88%*	89 *82%*
1	11 *14%*	6 *17%*	13 *9*	11 *15%*	24 *11%*	17 *16%*
total ≥1	12 *16%*	6 *17%*	16 *11%*	14 *19%*	28 *12%*	20 *18%*

*ITT population

Table 155. Trial 010: Asthma exacerbations in steroid reduction phase, observed (subjects, %)*

	Q2w		Q4w		Overall	
Number of exacerbations	Omlzmb *n=76*	Placebo *n=35*	Omlzmb *n=149*	Placebo *n=74*	Omlzmb *n=225*	Placebo *n=109*
0	68 *89%*	22 *63%*	130 *87%*	56 *76%*	198 *88%*	78 *72%*
1	7 *9%*	10 *29%*	13 *9%*	15 *20%*	20 *9%*	25 *23%*
total ≥1	8 *11%*	13 *37%*	19 *13%*	18 *24%*	27 *12%*	31 *28%*

*ITT population

Subgroup analyses of trial 010 exacerbations

Table 156. Trial 010: Age : Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		Stable steroid		Steroid reduction	
Age category (yrs.)		Omalizumab	Placebo	Omalizumab	Placebo
5-9	*n*	*106*	*49*	*106*	*49*
	% ≥1	14	18	16	41
10-12	*n*	*119*	*60*	*119*	*60*
	% ≥1	11	18	8	18

Table 157. Trial 010: Allergen sensitivities: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		Stable steroid		Steroid reduction	
# Allergens		Omalizumab	Placebo	Omalizumab	Placebo
0	n	0	0	0	0
	% ≥1	0	0	0	0
1	*n*	*29*	*19*	*29*	*19*
	% ≥1	10	11	14	37
2	*n*	*68*	*32*	*68*	*32*
	% ≥1	9	28	15	38
3	*n*	*58*	*29*	*58*	*29*
	% ≥1	16	10	12	21
4	*n*	*44*	*15*	*44*	*15*
	% ≥1	14	20	11	20
5	*n*	*26*	*14*	*26*	*14*
	% ≥1	15	21	4	21
	total	*225*	*109*	*225*	*109*

Table 158. Trial 010: Baseline BDP dose: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		Stable steroid		Steroid reduction	
BDP dose (µg/day)		Omalizumab	Placebo	Omalizumab	Placebo
168	*n*	*70*	*40*	*70*	*40*
	% ≥1	11	13	10	20
252	*n*	*34*	*19*	*34*	*19*
	% ≥1	12	26	9	37
336	*n*	*86*	*34*	*86*	*34*
	% ≥1	12	15	13	24
420	*n*	*26*	*10*	*26*	*10*
	% ≥1	19	20	8	50
	total	*216*	*103*	*216*	*103*

Table 159. Trial 010: Baseline % FEV_1: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		Stable steroid		Steroid reduction	
%FEV_1 quartile		Omlzmb	Placebo	Omlzmb	Placebo
≤74.00%	*n*	*63*	*24*	*63*	*24*
	% ≥1	21	29	16	38
74.01 to ≤84.00	*n*	*53*	*28*	*53*	*28*
	% ≥1	4	11	9	21
84.01 to ≤94.00	*n*	*57*	*28*	*57*	*28*
	% ≥1	14	14	11	36
>94.01	*n*	*52*	*29*	*52*	*29*
	% ≥1	10	21	12	21
	total	225	109	225	109

Table 160. Trial 010: Baseline IgE: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		Stable steroid		Steroid reduction	
IgE Quartile (IU/ml)		Omlzmb	Placebo	Omlzmb	Placebo
≤141	*n*	*49*	*35*	*49*	*35*
	% ≥1	8	11	20	14
141.01 to ≤241	*n*	*58*	*25*	*58*	*25*
	% ≥1	12	20	7	32
241.01 to ≤481	*n*	*62*	*22*	*62*	*22*
	% ≥1	16	23	15	36
>481.01	*n*	*56*	*27*	*56*	*27*
	% ≥1	13	22	7	37
	total	225	109	225	109

Table 161. Trial 010: Weight: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		Stable steroid		Steroid reduction	
Weight Quartile (kg)		Omlzmb	Placebo	Omlzmb	Placebo
≤29.10	*n*	*56*	*29*	*56*	*29*
	% ≥1	13	21	20	41
29.11 to ≤36.00	*n*	*59*	*24*	*59*	*24*
	% ≥1	10	25	10	42
36.11 to ≤45.00	*n*	*58*	*25*	*58*	*25*
	% ≥1	17	20	7	12
>45.01	*n*	*52*	*31*	*52*	*31*
	% ≥1	10	10	12	19
	total	225	109	225	109

Table 162. Trial 010: Doctor visits prior to trial: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		Stable steroid		Steroid reduction	
Doctor Visits		Omlzmb	Placebo	Omlzmb	Placebo
0	*n*	*98*	*41*	*98*	*41*
	% ≥1	6	15	5	20
1 or 2	*n*	*81*	*47*	*81*	*47*
	% ≥1	11	19	20	28
3-6	*n*	*34*	*19*	*34*	*19*
	% ≥1	29	21	12	42
>6	*n*	*12*	*2*	*12*	*2*
	% ≥1	25	50	17	100
	total	*225*	*109*	*225*	*109*

Table 163. Trial 010: Baseline total symptom score: Subjects (proportions of group) with 0 or any number of exacerbations--observed exacerbations

		Stable steroid		Steroid reduction	
		Omlzmb	Placebo	Omlzmb	Placebo
Total symptom score					
0	*n*	*64*	*23*	*64*	*23*
	% ≥1	8	17	6	39
0.08 to ≤0.5714	*n*	*49*	*29*	*49*	*29*
	% ≥1	12	17	18	24
0.5715 to ≤1.4615	*n*	*51*	*26*	*51*	*26*
	% ≥1	4	27	16	23
>1.4616	*n*	*59*	*30*	*59*	*30*
	% ≥1	24	13	10	27
	total	*223*	*108*	*223*	*108*

Table 164. Trial 010: Global evaluations of treatment effectiveness at the end of steroid reduction phase (proportions of subjects)

Rating	Subjects' evaluation			Investigators' evaluation		
	Omalizumab	Placebo	Difference	Omalizumab	Placebo	Difference
	n=256	*n=244*		*n=256*	*n=243*	
Excellent	35.3	17.5	17.8	31.5	16.3	15.2
Good	49.5	41.7	7.8	44.7	32.7	12
Moderate	10.1	20.4	-10.3	18.3	27.9	-9.6
Poor	4.6	19.4	-14.8	5	21.2	-16.2
Worsening	0.5	1.0	-0.5	0.5	1.9	-1.4

Trial 011

Trial 011 subgroup analyses

Table 165. Trial 011: Subjects (%) with 0 or any number of observed exacerbations by subgroup, inhaled corticosteroid users

Number of Exacerbations		Stable Phase				Reduction Phase			
		Omalizumab		Placebo		Omalizumab		Placebo	
		N	*%*	N	*%*	N	*%*	N	*%*
Race									
White	0	93	*88*	88	*87*	89	*84*	80	*79*
	1+	13	*12*	13	*13*	17	*16*	21	*21*
Black	0	0	*0*	1	*50*	0	*0*	1	*50*
	1+	0	*0*	1	*50*	0	*0*	1	*50*
Oriental	0	2	*100*	1	*100*	2	*100*	0	*0*
	1+	0	*0*	0		0	*0*	1	*100*
Other	0	18	*100*	15	*94*	18	*100*	14	*88*
	1+	0	*0*	1	*6*	0	*0*	2	*13*
% Predicted FEV_1 at visit 3									
≤80%	0	73	*88*	58	*85*	71	*86*	52	*76*
	1+	10	*12*	10	*15*	12	*14*	16	*24*
>80%	0	40	*93*	47	*90*	38	*88*	43	*83*
	1+	3	*7*	5	*10*	5	*12*	9	*17*
Sex									
Male	0	39	*87*	46	*90*	41	*91*	42	*82*
	1+	6	*13*	5	*10*	4	*9*	9	*18*
Female	0	74	*91*	59	*86*	68	*84*	53	*77*
	1+	7	*9*	10	*14*	13	*16*	16	*23*
Age (yr.)									
<17	0	10	*83*	8	*89*	11	*92*	6	*67*
	1+	2	*17*	1	*11*	1	*8*	3	*33*
18-64	0	93	*89*	92	*87*	89	*86*	85	*80*
	1+	11	*11*	14	*13*	15	*14*	21	*20*
65+	0	10	*100*	5	*100*	9	*90*	4	*80*
	1+	0	*0*	0	*0*	1	*10*	1	*20*
Number of positive allergens									
1	0	5	*83*	5	*83*	5	*83*	6	*100*
	1+	1	*17*	1	*17*	1	*17*	0	*0*
2	0	28	*85*	31	*76*	29	*88*	28	*68*
	1+	5	*15*	10	*24*	4	*12*	13	*32*
3	0	26	*96*	30	*97*	24	*89*	27	*87*
	1+	1	*4*	1	*3*	3	*11*	4	*13*
4	0	54	*90*	39	*93*	51	*85*	34	*81*
	1+	6	*10*	3	*7*	9	*15*	8	*19*

Table 166. Trial 011: Subjects (%) with 0 or any number of observed exacerbations by subgroup, inhaled corticosteroid users

Number of Exacerbations		Stable Phase				Reduction Phase			
		Omalizumab		Placebo		Omalizumab		Placebo	
		N	*%*	N	*%*	N	*%*	N	*%*
IgE Level (IU/ml)									
<94	0	24	*86*	19	*73*	23	*82*	19	*73*
	1+	4	*14*	7	*27*	5	*18*	7	*27*
94-<368	0	31	*94*	24	*89*	30	*91*	24	*89*
	1+	2	*6*	3	*11*	3	*9*	3	*11*
192-<368	0	31	*89*	28	*90*	28	*80*	26	*84*
	1+	4	*11*	3	*10*	7	*20*	5	*16*
368+	0	27	*90*	34	*94*	28	*93*	26	*72*
	1+	3	*10*	2	*6*	2	*7*	10	*28*
Body weight (kg)									
<62	0	35	*88*	22	*85*	35	*88*	18	*69*
	1+	5	*13*	4	*15*	5	*13*	8	*31*
62-<73	0	25	*96*	31	*89*	23	*88*	29	*83*
	1+	1	*4*	4	*11*	3	*12*	6	*17*
73-<85	0	20	*91*	24	*83*	19	*86*	20	*69*
	1+	2	*9*	5	*17*	3	*14*	9	*31*
85+	0	33	*87*	28	*93*	32	*84*	28	*93*
	1+	5	*13*	2	*7*	6	*16*	2	*7*
Inhaled Dose at Baseline (μg)									
≤1000	0	44	*94*	40	*83*	42	*89*	37	*77*
	1+	3	*6*	8	*17*	5	*11*	11	*23*
>1000 to 1500	0	40	*85*	42	*91*	42	*89*	40	*87*
	1+	7	*15*	4	*9*	5	*11*	6	*13*
>1500	0	29	*91*	23	*88*	25	*78*	18	*69*
	1+	3	*9*	3	*12*	7	*22*	8	*31*

Table 167. Trial 011: Global evaluations of treatment after the steroid reduction phase

Source of judgment		Inhaled		Oral	
		Omalizumab	Placebo	Omalizumab	Placebo
		n=119	*n=112*	*n=42*	*n=42*
Subject	Excellent	38 (32%)	19 (17%)	13 (28%)	9 (21%)
	Good	61 (51%)	46 (41%)	17 (37%)	15 (36%)
	Moderate	11 (9%)	24 (21%)	12 (26%)	6 (14%)
	Poor	9 (8%)	23 (21%)	4 (9%)	10 (24%)
	Worsening	0	0	0	2 (5%)
		n=119	*n=112*	*n=46*	*n=42*
Investigator	Excellent	26 (22%)	11 (10%)	8 (17%)	5 (12%)
	Good	63 (53%)	42 (38%)	16 (35%)	10 (24%)
	Moderate	24 (20%)	29 (26%)	16 (35%)	14 (33%)
	Poor	5 (4%)	30 (27%)	6 (13%)	11 (26%)
	Worsening	1 (1%)	0	0	2 (5%)

Trial Q2143g

Dosing chart

Table 168. Dosing chart for trial Q2143g (milligrams per 4-week interval)*

Interval	Baseline IgE (IU/ml)	Body mass (kg)								
		≥20-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
Q4w	>30-100	150	150	150	150	150	150	150	300	300
	>100-200	150	150	300	300	300	300	300	225	300
	>200-300	150	300	300	300	225	225	225	300	375
	>300-400	300	300	225	225	225	300	300		
	>400-500	300	225	225	300	300	375	375		
	>500-600	300	225	300	300	375				
Q2w	>600-700	225	225	300	375					
	>700-800	225	300	375						
	>800-900	225	300	375						
	>900-1000	300	375							
	>1000-1100	300	375							
	> 1100-1200	300	Do not dose without approval of Medical Monitor							
	>1200-1300	375								

*Note that while the format is different and the range of serum IgE is greater, the dosing for a 4-week interval is the same as for the critical efficacy trials and trials IA04 and 011.
*This dosing table was used after a protocol amendment about 1 year into the trial. Its only difference from the dosing table that preceded it is that the >90-150 kg body mass category was divided into two body mass categories.

Subgroup analyses

Table 169. Trial Q2143g: Subset analyses of observed exacerbations (% subjects with at least 1 exacerbation)*

Number of exacerbations	Control		Omalizumab	
	N	*%*	N	*%*
Race				
White	119	*25*	200	*21*
Black	29	*37*	39	*27*
Hispanic	13	*33*	14	*18*
Other	9	*45*	7	*18*
% predicted FEV_1 at visit 3				
≤60%	53	*41*	77	*31*
>60% to <80%	59	*25*	87	*21*
≥80%	58	*24*	96	*18*
Sex				
Male	68	*26*	105	*20*
Female	102	*29*	155	*23*
Age				
<17	28	*34*	34	*20*
18-64	133	*27*	206	*22*
65+	9	*26*	20	*24*
IgE (IU/ml)				
<70	44	*28*	68	*24*
70-<140	42	*28*	74	*23*
140-<250	37	*26*	46	*16*
≥250	47	*30*	72	*23*
Body mass (kg)				
<64	40	*29*	66	*23*
64-<78	40	*23*	48	*16*
78-<93	40	*28*	71	*22*
≥93	50	*32*	75	*25*

*Safety population

Table 170. Trial Q2143g: Days with various symptoms by questionnaire, safety population

			Control	Omalizumab
Cough or wheezing	Week 0	*n*	*618*	*1220*
		Mean ± sd	5.2 ± 5.3	5.5 ± 5.4
		Subjects with ≥1	479 (78)	960 (79)
	Week 24	*n*	*564*	*1080*
		Mean ± sd	4.2 ± 5.1	3.1 ± 4.4
		Subjects with ≥1	383 (68)	622 (58)
Activity slow or stop	Week 0	n	618	1220
		Mean ± sd	2.7 ± 4.5	2.7 ± 4.3
		Subjects with ≥1	286 (46)	612 (50)
	Week 24	n	564	1080
		Mean ± sd	2.0 ± 3.7	1.3 ± 3.1
		Subjects with ≥1	226 (40)	289 (27)
Missed School or work	Week 0	n	600	1177
		Mean ± sd	0.3 ± 1.4	0.2 ± 1.3
		Subjects with ≥1	55 (9)	86 (7)
	Week 24	n	544	1045
		Mean ± sd	0.3 ± 1.6	0.2 ± 0.8
		Subjects with ≥1	44 (8)	63 (6)
Plans Changed	Week 0	n	618	1220
		Mean ± sd	0.8 ± 2.1	0.6 ± 2.0
		Subjects with ≥1	122 (20)	206 (17)
	Week 24	n	564	1080
		Mean ± sd	0.8 ± 2.3	0.4 ± 1.7
		Subjects with ≥1	103 (18)	115 (11)
Limited Activity	Week 0	n	618	1220
		Mean ± sd	1.3 ± 3.2	1.1 ± 3.0
		Subjects with ≥1	164 (27)	266 (22)
	Week 24	n	564	1080
		Mean ± sd	1.1 ± 2.9	0.6 ± 2.1
		Subjects with ≥1	128 (23)	143 (13)

Trial IA04

GINA 1998 treatment steps

Table 171. Trial IA04: Guidelines for assessing step of treatment

GINA Classification

GINA treatment steps 1-4 (step 4 is classed as "severe persistent") for concomitant medication scoring were classified according to the definitions below:

Long term* Systemic corticosteriods (SCS) (irrespective of other con-meds) = step 4
Inhaled corticosteroids (ICS)** > 500 mcg but no SCS = step 3
Nebulized ICS is equivalent to > 500mcg (but no SCS) = step 3
ICS < 500 mcg but no Long acting Beta-2 agonist (LABA) step 2
ICS > 200 mcg with LABA step 3
Short acting beta-2 agonists (SABA) alone = step 1

*long term is > 10 days
** ICS based on Equivalent doses to 1000µg Beclomethasone dipropionate (BDP)

Note 1
[Maximum of step 2 without ICS (even if on alternative anti-inflammatory e.g. theophyline, cromone, anti-leukotrienes).]

Note 2
Where no start dates were available for ICS, i.e. all missing dates were confirmed as not available by the investigators, these patients were included in the analysis assuming they were receiving the reported ICS medication at Visit 2.

Note 3:
For ICS records which have a start and end date on Visit 2 the highest dosage was used to calculate the GINA classification and BDP equivalence.

Note 4:
If data for dosage and/or frequency is not available the patient was unclassified.

[Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NIH Publication No. 96-3659B, November 1998]